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COTTONSEED PROTEIN vs. COTTONSEED OIL SENSITIVITY

I. Background and Personal Experience

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THE title of this symposium, "Cottonseed Protein vs. Cottonseed Oil Sensitivity," is misleading. There is no incompatibility between cottonseed protein and cottonseed oil. In nature, these substances exist in a symbiotic combination, as it were. Mere man comes along and disrupts their union. The consequent cleavage has given rise to a sharp difference of opinion among allergists concerning the allergenic properties of cottonseed oil in contradistinction to those of the defatted cottonseed meal.

At the outset, permit me to state my position. Sensitiveness to cottonseed flour or meal and to cottonseed oil are two distinct clinical entities. Sensitiveness to one does not connote sensitiveness to the other. Finally, we have shown that edible cottonseed oil is free of the allergen existent in the meal.

Let us now bring the background to the fore. Brown[4] in 1929 reported an incidence of 6 per cent of positive reactors to cottonseed protein: "thirteen out of a total of 214 definitely sensitive patients tested." Four of these thirteen patients, who reacted to cottonseed, were also tested "cutaneously with a drop of pure cottonseed oil, with negative results." Brown surmised that the cottonseed oil used in testing was probably so refined that all traces of protein had been removed. This opinion was reaffirmed by expert witnesses who testified at a public hearing before the Administrator of the Federal Security Agency, held at Washington, D. C., during November, 1947, and January, 1948.

In 1931, Bowman and Walzer,[5] who had contributed a chapter dealing with atopens and other excitants in one of the early textbooks on allergy, made the following assertions: "The active principle in cottonseed is probably a protein. . . . The oil of cottonseed contains active atopen and may

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therefore induce symptoms as an inhalant, ingestant, or contactant." This opinion has profoundly affected medical thought and practice. Thus, patients who were found sensitive to the extract of cottonseed meal were cautioned against the use of food products of which cottonseed oil was an ingredient. This is exemplified by statements made by Taub[12] in 1934. The opinion, "The oil of cottonseed contains active atopen and may induce symptoms as an inhalant, ingestant and contactant," is re-echoed. "It is almost impossible," he added, "to state all uses to which cottonseed and its products may be put or to determine all forms in which the active atopen principle may cause trouble to the hypersensitive patient." Taub enumerated thirteen sources of cottonseed as an ingestant and included Wesson oil and Crisco in the list.

In 1937, Rowe furnished interesting statistics on food sensitizations. In his table No. 30—the number of 1- plus, 2-plus, 3-plus, and 4-plus reactions to individual food allergens in 500 patients who gave one or more positive reactions—cottonseed does not appear. In his table No. 31—positive and negative cutaneous reactions to foods to which clinical sensitization existed in a series of 175 patients—there is reported one positive and one negative reaction with cottonseed. In his work, however, three cases of sensitiveness to cottonseed oil are described. Then comes a startling statement from Rowe: "I have recently demonstrated cottonseed allergen in Wesson oil."

Two years later, in 1939, Spies, Bernton and Stevens[10] first announced the isolation of a protein allergenic fraction from the water-soluble constituents of cottonseed embryo. They designated the fraction CS-1. This fraction is composed of protein and polysaccharide. Subsequent investigations have firmly established the fact that the protein component is responsible for the specific allergenic activity of the meal. In the following year, these authors[2] described a series of experiments which justified the conclusion that the specific and exceedingly potent water-soluble allergen of the cottonseed embryo did not occur in refined cottonseed oil. In this study, patients highly sensitive to the cottonseed allergen, CS-1A, gave negative reactions to the refined, edible cottonseed oil on contact with the skin; on ingestion and on instillation into the conjunctival sac and upper respiratory tract. Cottonseed oil, in doses of two to three tablespoonfuls daily, was prescribed for five patients, and the quantities of the oil dispensed were, respectively: 100, 150, 200, 300, and 500 ml. In addition, three patients were given saltine crackers spread with a heaping tablespoonful of the hydrogenated cottonseed oil. One patient was provided with a one pound can of the hydrogenated oil, which was used liberally as a substitute for butter. The absence of ill effects was noteworthy. Finally, eight normal individuals received a single sensitizing injection of a cottonseed serum in a skin site on the upper arm. Six of the eight skin areas exhibited no detectable response following ingestion of cottonseed oil but reacted positively to the orally administered cottonseed allergen derived from the seed itself. The remaining two sites were negative.

The attempt was also made to detect the presence of the cottonseed allergen in the refined oil. Three liters of the oil were passed twice in droplet form through a narrow column of 100 ml. of water. The water extract was thereafter concentrated to a volume of 15 ml. No nitrogen was found in the concentrated aqueous extract by the Kjeldahl micromethod, nor was nitrogen detected by the most sensitive qualitative test available.[1] Both cutaneous and intracutaneous tests were performed with the water extract on four of our cottonseed-meal-sensitive patients, with negative results. Two recipients, moreover, were sensitized with a cottonseed serum of high titer. The two passively sensitized sites yielded negative results when tested with the same aqueous extract of the oil.

The authors are careful in stressing the point that their findings are not submitted as evidence that clinical sensitiveness to refined cottonseed oil may not be encountered. Accordingly, Swineford's assertion that there is not a single authentic case of cottonseed oil sensitivity recorded in the literature is, indeed, challenging.[11] Interestingly enough, Figley[7] presented details of two cases suspected of specific sensitiveness to cottonseed oil. A follow-up study of these two cases, however, revealed an inconsistency in their reactions to the ingestion of samples of cottonseed oil and of other vegetable oils, submitted in a mask manner. Accordingly, Figley has become skeptical as to whether his cases are truly those of sensitiveness to cottonseed oil.[8]

The failure of cottonseed oil to provoke skin reactions, even in patients sensitive to cottonseed meal, has been noted by Brown, Figley, Mitchell, Loveless and by ourselves. Moreover, reagins for cottonseed allergens in the two alleged cases of cottonseed oil sensitiveness, recorded by Figley, were absent. Consequently, the diagnosis of cottonseed oil sensitiveness must be based on ingestion test. It is the only available criterion of sensitiveness to this particular derivative of cottonseed. Moreover, the ingestion test can be misleading unless it is designed and conducted in a manner to assure reliable and significant data.

In 1947, Spain[6] wrote critically of what he regarded as inadequate food labeling. He protests, "The term 'vegetable' oil means little to the asthmatic highly allergic to cottonseed oil, but quite able to tolerate soy, peanut or corn oil." Cooke,[6] in discussing allergy of the skin, lists twenty-four foods as potential causes of urticaria. Cottonseed oil is the last article of food enumerated. "Among these foods," he continues, "it is difficult to say which is the most important or to grade them as to their relative frequency in provoking reactions." By inference at least, Cooke and Spain recognize the existence of cases of sensitiveness to cottonseed oil in their practice.

Nevertheless, our search for a patient sensitive to cottonseed oil continued; and the opportunity to study an alleged case of sensitiveness to the oil in the person of a distinguished allergist was as welcome as it was revealing. The details of this investigation will appear in a future publication.[3] It may not be amiss, therefore, to present a brief summary of our

findings. The patient was sure that all shortenings containing cottonseed oil caused abdominal discomfort—acute griping pain and diarrhea. Canker sores, edema of lips and occasionally hives were other manifestations of his allergic reaction to cottonseed oil. He was confident he could differentiate cottonseed oil from corn oil with some discomfort. We were unable, however, to demonstrate by passive transfer tests the presence of reagins for water-soluble cottonseed protein or for cottonseed oil in his serum. Accordingly, the ingestion experiments in which our collaborator participated provided a noteworthy sequel to the serological study. Samples of vegetable oils, which included corn oil, cottonseed oil and olive oil were submitted in trial doses. Neither the subject nor the dispenser of the oils was informed of the composition of the individual samples until the close of the tests. Five of the fourteen samples contained cottonseed oil but in no instance were symptoms of distress provoked by ingestion of them. His failure to discriminate between cottonseed oil and corn oil became evident.

Assured and reassured by the results of the ingestion test, our collaborator is now enabled to partake of foods with cottonseed oil as an ingredient. To an allergist of mature clinical experience, we express our thanks for the demonstration of the importance of the "blind-fold" technique in the diagnosis of food allergy.

Our studies of the allergic phases of the cottonseed problem have extended over a period of ten years. The dietary restrictions, imposed upon the 6 per cent of the allergic population who are sensitive to cottonseed flour or meal, seem to us unwarranted in the light of the newer knowledge. Any attempt to avoid the ingestion of cottonseed oil presents difficulties—almost insurmountable. The culinary utilization of the oil embraces so many of our every day articles of diet, of which shortenings, salad dressings, potato chips, fried chicken, fried fish, canned sardines and tuna fish, bakery and candy products and oleomargarine are familiar representatives. At this point, it is important that we reiterate our former position: "Our findings are not submitted as evidence that clinical sensitiveness to refined cottonseed oil may not be encountered." We do insist, however, that the diagnosis of such sensitiveness be based on adequate data.

In this present restless and uncertain age, the psychosomatic aspects of allergic states are being stressed by clinicians. The biochemist is equally concerned when in allergic conditions the psyche is separated from the soma and especially the stoma.

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COTTONSEED PROTEIN vs. COTTONSEED OIL SENSITIVITY

II. A Case of Cottonseed Oil Sensitivity

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BERNTON, Coulson and Stevens[1] and Figley[5] have recently reviewed the subject of sensitivity to edible vegetable oils with particular reference to the question of cottonseed sensitivity. They pointed out that allergists for the most part have made no distinction between sensitivity to cottonseed meal and cottonseed oil, and that it had been assumed by many that cottonseed oil contains sufficient traces of the highly potent cottonseed protein to cause allergic symptoms.

Bernton, Spies and Stevens[2] were the first to question this apparent relationship; they showed that the water-soluble active principle of cottonseed meal is not present in commercially available edible cottonseed oil or hydrogenated cottonseed oil and that patients who are clinically sensitive only to water-soluble cottonseed extractives may safely be spared the inconveniences of attempting to avoid cottonseed oil.

Although somewhat outside the scope of this particular presentation, our experience is in agreement with these fundamental observations of Bernton and his associates. We have no desire to enter this controversy, as reviewed by Figley[5] and presented in detail by several witnesses appearing before the public hearings held under auspices of the Federal Food and Drug Administration for the purposes of establishing definitions and standards of identity for salad dressings.[4]

Our aim in this communication is to cite evidence in favor of the existence of clinical sensitivity to cottonseed oil. In our cases of cottonseed oil sensitivity, to be presented herewith, there was no evidence of sensitivity to cottonseed protein as determined by the existence of positive skin tests with the water soluble fraction of cottonseed.

Case 1.—A physician, aged thirty-eight, had been subject to perennial nasal and sinus symptoms since 1927, unexplained chronic fatigue since 1928 and intermittent bouts of gastrointestinal symptoms, conjunctivitis and urgency and frequency of urination for the past decade. For the past six years he had complained of chronic muscle soreness and intermittently painful joints, although there had been no evidence of swelling, limitation of motion or x-ray abnormalities of the involved joints.

He was characteristically awakened in the middle of the night by insomnia and epigastric distress. All symptoms were accentuated on arising in the morning. He experienced a flare of fatigue, nervousness and abdominal distress beginning between two and three hours after each meal. He learned the most satisfactory manner by means of which temporary relief could be obtained from these symptoms was to eat additional food at the time of their onset. The satiation of this voracious ap-

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petite for interval feedings resulted in the development of moderate obesity and the apparent inability to follow a reduction type of diet. He also learned that foods containing corn were most effective in bringing about this temporary degree of relief.

The patient was aware that peaches, oranges, coffee, chocolate and Coca-Cola increased his gastrointestinal distress, and the ingestion of lemon or tea was followed by increased irritability and nervousness.

A diagnosis of hypoglycemia had been suspected repeatedly, but this interpretation of his symptoms had not been confirmed by diagnostic laboratory data. Although he frequently had a purulent discharge from the prostate, conjunctivae and sinuses, chronic infections involving these areas could not be demonstrated.

Aside from moderate obesity and pale, boggy nasal mucous membranes, his physical examination was within normal limits.

An allergic study revealed skin test evidence of sensitivity to house dust, feathers and orris root. A scratch test with cottonseed extract was negative; other skin tests with foods were not performed.

An individual food test with corn (according to Rinkel's technique[9] as modified slightly by Randolph and Rawlings[8]) was followed by a sharp immediate increase of his fatigue and gastrointestinal distress. A similar test with potatoes was followed in thirty minutes by the chilliness, sneezing and rhinorrhea. Sensitivity to chocolate and grape was determined on the basis of similar direct evidence. Individual food tests with other major foods were not associated with reactive symptoms.

In spite of the maintenance of inhalant therapy and the avoidance of foods incriminated at this stage of the diagnosis, he had only partial relief of his chronic allergic symptoms.

Sensitivity to cottonseed was suspected during the course of avoiding milk prior to performing an individual food test with this food, as he felt decidedly worse during this period in which he had materially increased his intake of home-made mayonnaise prepared from Wesson oil. His suspicion of cottonseed sensitivity was further aroused when he observed that his headache, fatigue and general irritability were accentuated following meals containing cottonseed oil. The individual ingredients of the home-made salad dressing were then omitted four days each and tolerated when returned to the diet with the sole exception of cottonseed oil. The trial ingestion of 15.0 c.c. of Wesson oil was followed by the prompt occurrence of headache and abdominal distress. He reported marked improvement following the avoidance of cottonseed-containing products. He then returned cottonseed oil to his diet in the previously ingested amounts, continuing his other dietary measures as outlined, and on the second day reported the recurrence of frequent to continuous headaches, general logginess and marked fatigue.

He was then instructed in the absolute avoidance of all cottonseed oil for four days prior to the performance of an individual food test with 15.0 c.c. of commercial Wesson oil. Ten minutes following the test feeding, he developed a sharp headache coincident with the complaint of a "rock-like" sensation in the abdomen. Variations of the total leukocyte counts following this test are shown in Figure 1. Residual weariness to an extreme degree persisted for an additional twenty-four hours.

He then avoided all sources of cottonseed oil, eating only food prepared in his own home. He remained free of allergic symptoms under these circumstances, but on each occasion that he ate away from home for a few consecutive meals he had a recurrence of his headache and fatigue within one to three days even though he attempted to avoid cottonseed and other incriminated foods. On several different occasions he developed a recurrence of cramping sensations in his leg muscles and other described constitutional symptoms following the ingestion of food subsequently learned to have been prepared with cottonseed oil.

It should be stated that similar symptoms were known to follow the ingestion of corn. However, it has been clearly shown that the test or inadvertant ingestion of

cottonseed oil in the absence of corn intake has repeatedly produced the symptomatology in question.

After a year of avoiding cottonseed except for an occasional contact incident to attending medical meetings, he has developed a slight degree of tolerance to cottonseed oil in that a single feeding in the amounts obtained by chance may now be taken

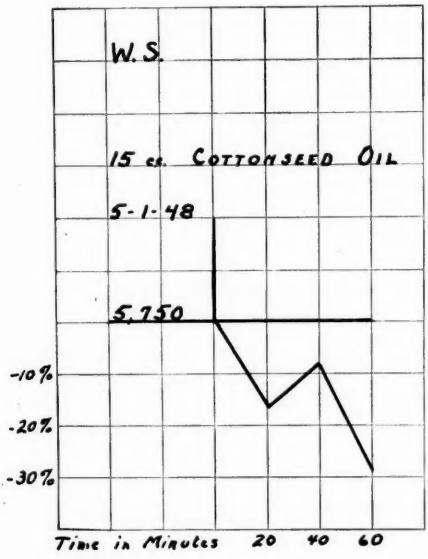

Fig. 1. Variations in the total leukocyte counts following the experimental ingestion of 15.0 c.c. cottonseed (Wesson) oil.

without the recurrence of symptoms. The ingestion of small amounts in repeated feedings still results in the redevelopment of headache, fatigue and irritability. The trial ingestion of cottonseed meal has not been attempted.

It is of further interest that he has had no joint symptoms during the past year except after the use for a week of a brand of bread known to have been corn-free and thought to have been made with lard but subsequently found to have contained cottonseed oil.

Case 2.—E. R., a housewife, aged fifty-four, had been subject to severe headaches for fifteen years, during the past decade of which she had complained of constant headaches, dizziness and myalgia of the posterior cervical muscles and upper back. When first seen in 1946, she also complained of a debilitating degree of weakness, chronic dermatitis of her hands and alternating constipation and diarrhea.

Her clinical history of house dust sensitivity was confirmed by positive skin tests with house dust extract, specific therapy having been helpful in controlling a part of her symptomatology. She was shown to have a widespread allergic response to foods, indicated by the precipitation of acute clinical reactions following the experimental ingestion of several articles of the diet in accordance with the technique of the individual food test.[8,9]

The maintenance of house dust therapy, the avoidance of silk and incriminated

foods, and the use of other foodstuffs on a rotating schedule[10] were effective in relieving her chronic symptoms for a period of several months.

In early 1948 she reported a gradual recurrence of symptoms in spite of strict adherence to her previously effective environmental and dietary control. She was subjected to several other individual food tests including cottonseed oil. Following the

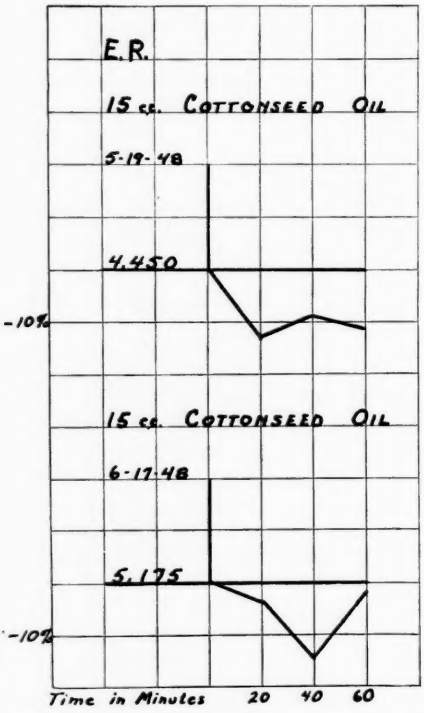

Fig. 2. Variations in the total leukocyte counts on each of two occasions following the experimental ingestion of 15.0 c.c. cottonseed (Wesson) oil.

avoidance of cottonseed in all forms for four days she ingested 15.0 c.c. of Wesson oil experimentally. Thirty minutes later she complained of marked sleepiness and at forty minutes developed a mild frontal headache; these symptoms became progressively severe during the remainder of the day, in association with the development of drawing, aching pains in the lower back, and extreme fatigue. The morning following the cottonseed oil test, her back was so stiff and sore that it was necessary to be assisted in arising from bed. She remained extremely constipated for the three following days.

Two months later she was again subjected to a cottonseed oil test, again taking 15.0 c.c. of Wesson oil fasting, after having avoided cottonseed oil since her previous test. She noticed the onset of yawning and sleepiness beginning thirty-five minutes later; this was followed shortly by nausea, abdominal distress and tautness, pulling and drawing sensations of the posterior cervical muscles. Ninety minutes after the

test ingestion of cottonseed oil she developed a headache. During the afternoon of the test she complained of nausea, abdominal cramps and passed several diarrheic stools. Her gastrointestinal symptoms and extreme fatigue persisted for an additional two days.

During the past year she has found it necessary to avoid cottonseed oil completely, for each of several times that it has been ingested in small amounts inadvertently she has had a recurrence of headache, myalgia and fatigue. If taken in a larger quantity she experienced abdominal cramps and diarrhea.

Variations in the total leukocyte counts following these two tests are illustrated in Figure 2.

DISCUSSION

In addition to well-recognized allergic manifestations, both patients presented the symptoms of chronic fatigue and myalgia, first recognized as of allergic origin by Rowe[12,13] and subsequently reviewed by one of us.[6,7] The second patient also had joint manifestations highly suggestive of early arthritis which responded to allergic management in a manner similar to those recently reported by Zeller.[15] Both individuals had the typical timing of their chronic symptoms at specific times of the day indicative of the masked symptomatology of chronic food allergy as described by Rinkel.[11]

We believe that the data herewith presented may be interpreted in only one way, namely, that these two individuals are clinically sensitive to cottonseed oil as it is found in commercial foods.

The question of whether the symptoms in these cases might be explained on the basis of corn oil as an inadvertent contaminant of cottonseed oil must be raised in view of the well-known commercial practice, in at least certain oil refineries, of employing the same equipment in refining both cottonseed oil and corn oil, and the fact that both of these patients were clinically sensitive to corn. This question has been discussed with technicians familiar with refinery processes. There was agreement that while there might be such a contamination in an occasional lot, this would certainly not be true in the vast majority of cottonseed oil specimens. The consistency with which the ingestion of cottonseed oil has been followed by the development of clinical symptoms in these patients would make it highly improbable that the symptoms were caused by the ingestion of corn oil as a contaminant.

Doubt has been expressed in certain quarters as to the allergenicity of refined vegetable oils. It is agreed that the oil fractions of foods cause allergic symptoms less frequently than other refined food products and that many patients sensitive to whole foods are able to tolerate specific refined oils in cumulative feedings without developing clinical responses. There are numerous instances, however, in which refined vegetable oils are known to produce allergic symptoms. Duke[3] was the first to point out the allergenicity of soy bean oil, and Rowe[14] has incriminated cottonseed,* corn, peanut and olive oils. In our clinical experience, the experimental ingestion of

*Dr. Albert H. Rowe has recently informed us that his case of allergy to cottonseed oil also failed to show skin reactions to cottonseed protein. He has also recently re-established the fact that the ingestion of cottonseed oil continues to cause allergic symptoms in this patient.

corn oil and peanut oil have been shown to cause allergic reactions in certain instances in which other fractions of the same foods were known to be allergenic. Although we have tested several patients with skin test and clinical evidence of sensitivity to cottonseed meal, as yet we have not been able to induce allergic responses when these same individuals were experimentally fed commercially available cottonseed oil. Our experience in this respect confirms the statements of Bernton, and associates[1,2] Figley[5] and others.

It should be re-emphasized that the cases of apparent sensitivity to cottonseed oil, herewith reviewed, differ from those previously reported in that these individuals react with allergic manifestations following the ingestion of cottonseed oil but fail to give positive skin tests with extracts of cottonseed protein.

The incidence of this type of cottonseed sensitivity would seem to be relatively rare as we have encountered only two cases in approximately seventy-five patients who have been subjected to individual food tests with cottonseed oil (Wesson oil). The possibility of cottonseed oil sensitivity was suspected only in those patients who continued to have unexplained allergic symptoms after two months of diagnostic food studies, during which time all previously incriminated articles of the diet had been avoided.

In each instance all cottonseed products were scrupulously avoided for a period of four days prior to the experimental ingestion of cottonseed oil. Care was taken to conduct the preliminary period of specific avoidance at a time when the patient was able to prepare and eat all meals at home. The technique of the individual food test is that described by Rinkel[9] and modified slightly by Randolph and Rawling.[8] In the two positive cases it may be observed that the criteria for the existence of specific sensitivity were based primarily on the precipitation of allergic symptoms, although in each instance there was an associated decrease of the total leukocyte counts (Figs. 1 and 2). The significance of the variation of the total leukocyte levels in the individual food test has been discussed elsewhere.[8]

SUMMARY

Two cases of cottonseed oil sensitivity in the absence of sensitivity to cottonseed protein, as determined by negative skin tests with extracts of cottonseed, are reported.

In both instances, the experimental or inadvertent ingestion of cottonseed oil as encountered in commercially available foods has been shown to result in the production of allergic symptoms.

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COTTONSEED PROTEIN vs. COTTONSEED OIL SENSITIVITY

III. The Atopen Content of Cottonseed Oil

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THE purpose of this investigation was to determine whether the atopen of cottonseed could be detected in crude cottonseed oil, or in any of the various stages of refinement of the oil, and if so, whether the refining processes altered the atopen content.

In the present study, samples of cottonseed oil were obtained from each of the stages of commercial refinement. Extracts were prepared by various methods from each of these oil samples, suitable for intracutaneous testing. The presence of the cottonseed atopen was then detected in these extracts by the Prausnitz-Kustner technique, using a high titered cottonseed serum of known strength.

DESCRIPTION OF COTTONSEED OIL SAMPLES

The cottonseed oils used in this investigation were specimens from each of four stages of commercial refining. The samples were supplied by the National Cottonseed Producers' Association, through courtesy of Dr. Henry Stevens. This material consisted of four samples which were labeled as follows: Oil 1—crude oil; oil 2—alkali refined oil; oil 3—bleached oil; oil 4—deodorized oil. In addition, a fifth sample—Wesson oil—was obtained by the purchase of an original container on the open market, and so labeled.

PREPARATION OF EXTRACTS

Extracts suitable for intracutaneous testing were prepared from these five samples of cottonseed oil by various methods. Different proportions of oil, chloroform and diluent, 5/10 per cent phenol in normal saline, were agitated and allowed to stand for varying periods. The water soluble fraction was sterilized and used for testing. The procedures were tabulated in Table I. A summary of this table revealed that the most potent extracts were obtained when two parts each of the respective oil and chloroform were added to one part diluent, agitated fifteen minutes, and allowed to stand forty-eight hours at 10° C.

STANDARDIZATION OF SERUM

The serum used in the present study was obtained from a patient, M.C., who presented a marked clinical sensitivity to cottonseed. This serum was

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TABLE I. PREPARATION OF EXTRACTS

Extract Number	Oil Sample	Oil c.c.	Chloroform c.c.	Diluent c.c.	Mixing Time Minutes	Extracting Time Hours	Sterilization	Extract Activity
1*	1	10	50	50	15	12	S	Moderate
2*	1	10	50	50	15	24	S	Moderate
3*	1	10	35	35	15	12	S	Moderate
3A**	1	10	35	35	15	12	S	None
4***	2	10	50	50	15	24	T	Slight
4A****	2	10	50	50	15	24	T	None
5	1	10	50	50	25	72	T	None
6	3	10	20	20	30	12	T	Slight
7	4	10	20	20	30	12	T	Slight
8	2	10	20	20	60	12	T	Slight
9	3	10	20	20	60	12	T	Slight
10	4	10	20	20	60	12	T	Slight
11	5	20	20	10	10	12	S	Moderate
14	2	20	20	10	15	48	S	Marked
15	4	20	20	10	15	48	S	Moderate
16	2	30	20	5	10	12	S	Moderate
17	3	30	20	5	10	12	S	Moderate
18	4	30	20	5	10	12	S	Moderate
19	5	30	20	5	10	12	S	Moderate

*Formed 3 fractions after agitation.
**A second aqueous fraction collected from Ext. 3 on standing an additional 12 hours.
***Formed 2 fractions after agitation; aqueous fraction formed in 12 hours.
****Extract 4, in part, was concentrated to 4 c.c. by evaporation by fanning.
S Sterilized by Seitz filtration.
T Sterilized by covering with toluol and allowing to stand 72 hours at 10° C.

standardized by the serum dilution method of Coca and Grove,[3] and the atopen dilution method of Levine and Coca.[4]

Serum Dilution Method.—Serial dilutions were made with M.C. serum in normal saline, as follows: 1:4; 1:16; 1:256; 1:1024; 1:4096. Skin sites on two normal subjects were sensitized with these respective dilutions. Refractoriness of the site was eliminated by allowing an interval of four days between sensitizing and testing. The subject was instructed *not* to ingest cottonseed in any form.[5] Nonspecific cutaneous reactions were ruled out by testing some of the sensitized sites with diluting fluid. The remaining sensitized sites were tested with about .02 c.c. each of a cottonseed extract containing .01 mg. of total N per c.c. It was found that this serum transferred a cottonseed sensitivity in a dilution of 1024, but not of 4096.

Atopen Dilution Method.—M.C. serum in undiluted form was used to sensitize about six skin sites each on two nonatopic subjects. Nonspecific cutaneous reactions and refractoriness of the site were ruled out as before. The subject was instructed *not* to ingest cottonseed in any form. A standardized cottonseed extract was serially diluted to contain respectively .000,01, .000,001, .000,000,1 and .000,000,01 mg. of total N per c.c. and tested on these sensitized sites. It was found that the atopen of cottonseed was definitely detected in a dilution containing .000,001 mg. of N per c.c. Testing with the next greater dilution gave doubtful reactions, and testing with further dilutions were negative. The result of this standardization showed that the atopen of cottonseed was definitely detected in an extract containing .000,001 mg. of total N of cottonseed per c.c. by use of this serum and with this technique.

TABLE II. PASSIVE TRANSFER TESTS
WITH EXTRACTS PREPARED FROM COTTONSEED OILS

Subject	Age	Extract	Oil	Reaction Sensitized Site		Reaction Control Site		Degree of Reaction
1	38	1	1	Sl—	6	Neg+	2	4
2	42	1	1	Sl+	10	Sl	8	2
2	42	13	1	Sl+	10	Sl	8	2
3	35	4	2	Sl	8	Neg	0	8
4	30	7	4	Sl	8	NegSl	4	4
5	17	9	3	Neg+	2	Neg+	2	0
5	17	10	4	NegSl	4	Neg	0	4
6	38	14	2	Sl+	10	NegSl	4	6
6	38	15	4	Sl+	10	NegSl	4	6
7	21	11	5	NegSl	4	Neg+	2	2
8	44	15	4	Sl+	10	NegSl	4	6
9	24	14	2	Sl+	10	Neg	0	10
10	25	11	5	Sl+	10	Neg	0	10
11	24	14	2	SlMod	12	Neg	0	12
11	24	14	2	SlMod	12	Neg	0	12
12	20	14	2	Sl—	6	Neg	0	6
12	20	15	4	NegSl	4	Neg	0	4
12	20	11	5	Sl	8	Neg	0	8
13	25	16	2	NegSl	4	Neg	0	4
13	25	17	3	Neg+	2	Neg	0	2
14	20	17	3	NegSl	4	Neg+	2	2

Degrees of Reaction with Numerical Equivalent

Reaction*	Neg	Neg+	NegSl	Sl—	Sl	Sl+	SlMod	Mod	Mod+	Mod	Mkd	Marked
Number	0	2	4	6	8	10	12	14	16	18		20

*Reaction—Combined evaluation of wheal, erythema and pruritus.

DETECTION OF COTTONSEED ATOPEN IN UNKNOWN EXTRACTS

The atopen content of the extracts prepared from the samples of cottonseed oil was next determined by use of this high titered serum by the Prausnitz-Kustner technique, but according to the refinements of indirect testing described by Walzer.[2,6] The subjects selected were young, nonatopic individuals with normally reacting skins.[7] The reactivity of the skin of each subject was determined by preliminary direct intracutaneous tests with extracts of ragweed, timothy, horse dander, and house dust. These subjects were next sensitized with undiluted M.C. serum in multiple sites, placed transversely across the upper outer aspect of the arm, 2 inches apart.[1] Each site was encircled with fountain pen ink to insure its future location. The subject was instructed *not* to ingest cottonseed in any form. Refractoriness was eliminated by an interval of four days between sensitizing and testing. Nonspecific reactions were ruled out by testing some of the sensitized sites on each subject with saline and extracts of corn and peanut. The remaining sensitized sites on each subject were intracutaneously tested with about .01 c.c. of the various extracts prepared from the samples of cottonseed oil, and a control test of the same size and with the same extract was injected into the unsensitized skin about 3 inches distal to the sensitized site. The reactions were noted in thirty minutes. A test was considered positive when there was an excess of reaction on the sensitized site when compared with the control. Tests were recorded in terms of ten degrees of positive reactions. To facilitate graphic comparison a number was assigned each degree of reaction. The final reaction was the numerical difference between the degree of reaction on the sensitized and controlled sites (Table II).

TABLE III. COMPARING THE ATOPEN CONTENT OF CRUDE AND REFINED COTTONSEED OILS

Subject	Age	Extract	Oil	Reaction Sensitized Site		Reaction Control Site		Degree of Reaction
6	38	14	2	Sl +	10	NegSl	4	6
9	24	14	2	Sl +	10	Neg	0	10
11	24	14	2	SlMod	12	Neg	0	12
11	24	14	2	SlMod	12	Neg	0	12
12	20	14	2	Sl—	6	Neg	0	6
6	38	15	4	Sl +	10	NegSl	4	6
8	44	15	4	Sl +	10	NegSl	4	6
12	20	15	4	NegSl	4	Neg	0	4

Degrees of Reaction with Numerical Equivalent

Reaction*	Neg	Neg +	NegSl	Sl—	Sl	Sl +	SlMod	Mod	Mod +	Mod	Mkd	Marked
Number	0	2	4	6	8	10	12	14	16	18		20

*Reaction—Combined evaluation of wheal, erythema and pruritus.

Twenty-one tests were made on fourteen subjects with ten different extracts, prepared from the five samples of oil. A summary of this table revealed that the crude oil had three extracts prepared from it, which were tested on three subjects, each of which gave a slight but definite positive transfer, with a reaction value of about 3. The alkali refined oil was tested on seven subjects, by two extracts. Each test gave a definite positive transfer with a reaction value of 9. The deodorized oil had two extracts prepared from it, which were tested on three subjects. The reaction value was about 2. The bleached oil had three extracts prepared from it which were tested on five subjects. Each test was positive, with a reaction value of about 5. Wesson oil had one extract prepared from it which was tested on three subjects. Each test was positive with a reaction value of 6. These results showed that the atopen of cottonseed was detected in the crude oil, and also in the various stages of processing the oil.

EFFECT OF REFINING PROCESSES ON ATOPEN CONTENT OF THE OIL

To determine whether the refining processes altered the atopen content of these oils, the alkali refined oil was compared with the refined bleached oil by the same technique. Extracts 14 and 15 were used in this comparison, both of which were prepared by the same method. The results were tabulated in Table III. Examination of this table revealed that the crude alkali refined oil, represented by extract 14, was tested on four subjects. Each transfer test was positive, with an average reaction value of about 10. The refined bleached oil, represented by extract 15, was tested on three subjects. Each test was positive, and the average reaction value was about 6. From these results it was apparent that the refining processes of cottonseed oil may diminish the atopen content of cottonseed slightly, but does not destroy the active principle.

SUMMARY AND CONCLUSIONS

1. The atopen of cottonseed was detected in the samples of crude and refined cottonseed oil by use of this serum and with this technique.

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COTTONSEED PROTEIN vs. COTTONSEED OIL SENSITIVITY

IV. An Objective Approach to the Diagnosis of Food-Allergy as Applied to Cottonseed Atopy

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IT is common knowledge that an *adequate* amount of allergen must be present in a given exposure for the allergic patient to develop symptoms, and that the minimal requirement varies with the individual. It is surprising, therefore, that so little information is available concerning what might be called a "minimal provocative dose" of an allergen. Physicians have preferred to judge their subjects' susceptibilities by means of tests carried out in the skin, even though it may not participate in the clinical disorder. The reasons for this are, no doubt, the ready availability of the dermis and the difficulty of arranging for uniform, graduated exposures to such allergens as pollens. It appealed to the author that food allergy could be evaluated through ingestion-tests carried out with graded doses of chemically standardized, food extract. The need for some such test became apparent during hearings before the U. S. Food and Drug Administration in 1947 and 1948, when the labeling of salad oils and dressings was discussed with particular reference to cottonseed as an allergen.[1] Although the expert witnesses agreed that this seed is highly allergenic, both by clinical and cutaneous tests, no one could state whether the small residue of protein in refined cottonseed oil is theoretically adequate to disturb the seed-allergic consumer.

In view of this situation, the present investigation was instituted in order to determine the tolerance of four cottonseed allergic adults for ingested cottonseed extract. Since it was desirable to relate the new procedure to conventional tests described in the literature, cutaneous, conjunctival and serological methods were also applied concurrently in such a manner as to elicit threshold responses. Having thus determined the minimal provocative requirements by various routes, we were in a position to establish a ratio between ingestive and other tissue tolerances, thereby endowing the latter tests with clinical significance. Furthermore, one could now evaluate the possible allergenic contamination of the oil by the performance of cutaneous and ingestion tests with the oil and its aqueous washings, any positive findings being matched against reactions obtained with known amounts of standardized extract.

MATERIAL AND METHODS

Patients.—Three healthy women, in their third and fourth decades, and one man in his twenties proved to be highly sensitive to the water-soluble

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constituents of cottonseed by clinical history and by several specific tests. Three of the group were also hypersensitive to pollens whereas the fourth was nonallergic except for a cutaneous reactivity toward house dust. Their histories are briefly recorded below.

duV.—This woman promptly develops itching and edema of her lips, tongue and throat after eating certain brands of doughnut, rolls and coffee-cake. She once exhibited a spectacular series of allergic reactions after tasting candy which was later found to contain a trace of cinacoa, or cottonseed flour. Within a few minutes, tingling and edema were noted in the mouth and throat; generalized urticaria soon occurred, followed by acute rhinitis, wheezing, nausea, vomiting and abdominal colic. She is clinically allergic to grass pollens as well as to cottonseed.

Sen.—Within fifteen minutes after eating a certain brand of white bread sold by a chain grocer, or certain kinds of doughnut, this woman regularly develops bronchial asthma. Upon nearing a couch upholstered with crude cotton wadding, she wheezes and becomes mildly dyspneic. During a course of immunization, she became violently asthmatic within half a minute after receiving a minute dose of cottonseed extract on several occasions. Indeed, her skilled allergist abandoned this form of therapy because of her extreme intolerance.

Woo.—Certain cookies, doughnuts, and breads provoke allergic dermatitis. Proximity to a couch upholstered with crude cotton padding results in wheezing. Therapeutic injections with cottonseed extract have produced generalized urticaria, marked asthma and hay fever within ten minutes on several occasions.

Sac.—This man does not appear to be as intensely sensitized toward cottonseed as the others, but has noted that he wheezes quite badly within ten minutes after lying on a cotton mattress. The ingestion of certain cookies and doughnuts leads to nausea.

All four subjects tolerate foods shortened with or fried in cottonseed oil or hydrogenated oils, as well as salad dressings made with the seed oil.

Tests.—Conjunctival, intracutaneous and scratch, serological.

After ether-defatted cottonseeds had been extracted in alkaline saline solution, the supernate was standardized on the basis of its phosphotungstic-acid-precipitable nitrogen, one-tenth milligram of nitrogen representing 10,000 "protein" nitrogen units (P.N.U.). A series of two-fold dilutions was prepared for testing purposes. The threshold response was then elicited in the eye of each patient by means of graded strengths of extract which were successively dropped into the conjunctival sac from a 26-gauge needle at five-minute intervals until slight reddening and itching were pro-

duced.[2] The same preparations were used to provoke threshold responses in the skin, 0.02 milliliter being introduced intracutaneously in graduated strengths and in duplicate. For scratch tests, a series of incisions about 1 milliliter long and 3 inches apart were made with a fine hypodermic needle along the flexor surface of each forearm. Appropriate strengths of extract were applied to these until the threshold reaction appeared. In the case of the oil, not only was this product rubbed gently into similar scratches, but so also were washings derived by shaking a large measure of this oil with one-tenth or one-sixtieth its volume of physiological saline.

The Prausnitz-Kustner, or indirect cutaneous, test was done in the usual manner; viz., 0.1 ml. of serum was intracutaneously injected into normal skin and the site was injected after twenty-four hours with .03 ml. of extract, the strength of which was just adequate to provoke an approximately maximal response.

In other sensitization experiments, a series of tubes was set up with a constant measure of serum and increasing strengths of cottonseed extract. Sites of normal skin were then injected with these serum-allergen combinations, to be tested next day with more antigen (.03 ml. of 10-unit extract). Any sites responding to this secondary test had obviously not been desensitized by the amount of antigen included in the original mixture. The first unresponsive site provided the index to the neutralization requirement for the serum in question.

Ingestion Tests.—Cottonseed extract. Before this test, the patient was told that he would be given either diluent or diluted cottonseed extract to swallow but would not learn the true identity until the experiment had been concluded. When the testing material was seed extract, 100-unit material was first tried, a measure being placed on the tongue from a 1 ml. syringe. In thirty minutes 1000-unit solution was employed and finally, if necessary, 10,000-unit extract. Each dose of one ml. or less was swallowed with the aid of water taken from a glass. The test was interrupted when definite allergic symptoms developed.

The procedure was similar when the oil of cottonseed, or a control material such as corn oil, was to be tested by ingestion, the only exception being that the entire volume was administered in one feeding since little or no reaction was to be expected.

FINDINGS

The results of the threshold tests are summarized in Table I, the provocative doses being expressed in terms of "protein" (P.N.) units of phosphotungstic-acid-precipitable nitrogen. Table II gives the equivalent in micrograms of precipitable nitrogen. It also indicates the ratios found when the threshold level revealed by ingestion was divided by that determined through tests of the eye, skin or serum.

TABLE I. COMPARISONS BETWEEN AMOUNT OF COTTONSEED EXTRACT REQUIRED FOR THRESHOLD RESPONSE BY INGESTION AND BY VARIOUS OTHER ROUTES

Expressed in Units of Phosphotungstic-Acid Precipitable Nitrogen

Case	Ingestion Test	Conjunctival Test		Intracutaneous Test		Passive Transfer Tests			Scratch Test
						Indirect Skin Test		Neutralization	
	Amount* in units	Strength** in units	Amount* in units	Strength** in units	Amount* in units	Strength** in units	Amount* in units	Amount* in units	Strength** in units
duV	128	5	0.09	0.000,035	0.000,000,7	0.156	0.0047	20	2.5
Sen	2,000	7½	0.14	0.000,008	0.000,000,2	0.156	0.0047	80	1.0
Woo	1,000	20	0.37	0.000,032	0.000,000,6	0.156	0.0047	20	5.0
Sac	10,000	100	1.11	0.000,300	0.000,006	1.25	0.038	30	100.0

*Actual amount involved in test, calculated by multiplying volume x strength (PNU or phosphotungstic-acid-precipitable nitrogen).
**PNU per ml.

TABLE II. COMPARISONS BETWEEN AMOUNT OF COTTONSEED EXTRACT REQUIRED FOR THRESHOLD RESPONSE BY INGESTION AND BY VARIOUS OTHER ROUTES

Expressed in Micrograms

	Ingestion Test	Conjunctival Test		Intracutaneous Test		Passive Transfer Tests				Scratch Test	
						Indirect Skin Test		Neutralization			
	Amount*	Amount*	Ratio†	Amount*	Ratio†	Amount*	Ratio†	Amount*	Ratio†	Strength**	Ratio†
duV	1.28	.0009	1,400	.000,000,007	183,000,000	.000,047	27,000	0.2	6.4	.025	51
Sen	20	.0014	14,000	.000,000,002	10,000,000,000	.000,047	425,000	0.8	25.0	.01	2,000
Woo	10	.0037	2,800	.000,000,006	1,700,000,000	.000,047	212,000	0.2	50.0	.050	200
Sac	100	.0111	9,000	.000,000,060	1,700,000,000	.000,375	270,000	0.3	333.0	1.00	100
Range of Ratios			1,400-14,000		183,000,000-10,000,000,000		27,000-425,000		6.4-333.0		51-2,000

*Actual amount involved in test, calculated by multiplying volume x strength (micrograms of phospho-tungstic-acid precipitable nitrogen).
**Micrograms per ml.
†Ratio of ingestion threshold to specified threshold.

duV.—Within several minutes of swallowing 0.1 ml. of extract containing 1280 P.N. units per ml., this woman developed slight sneezing and pruritus of her left lower lid. Thirty minutes after the first dose, she was given the same volume of 10,240-unit extract which shortly led to marked itching of the mouth and throat, flushing of the face and neck, and slight nausea. Her minimal requirement was assumed to have been met by the first ingestion, namely, 128 P.N.U. or 1.28 micrograms of precipitable nitrogen.

When increasingly strong extract was instilled into the conjunctival sac at five-minute intervals, a beginning erythema and pruritus of the eye were produced after extract containing 5 units per ml. had been employed. Since a fully rounded drop from a 26-gauge needle contains 1/54 of a ml., the actual amount instilled in this threshold test was 1/54 x 5 or .0925 unit. When this figure in micrograms was divided into the amount required for the ingestion response, it appeared that 1400 times more antigen was needed for the clinical than for the conjunctival reaction (Table II).

An even greater difference existed between the ingestion requirement and the allergen needed for the intracutaneous response. Here extract containing only .000,035 P.N. units per ml. excited the minimal reaction when injected in a volume of .02 ml. The actual provocative dose was, therefore, 1/50 of this figure, or 0.000,000,7 units. Table II reveals that by ingestion, 183 million times more had to be taken for a threshold response.

When serological studies were carried out in sites of normal skin which had been sensitized with 0.1 ml. of serum, it was found that much larger quantities of cottonseed extract than those referred to above had to be injected to elicit the first nearly maximal response, 0.156-unit extract proving effective. Even here, however, the requirement was 1/27,000 of the ingestion test. To exhaust the serum of its sensitizing capacity, cottonseed extract had to be added to it in the proportion of 20 units to 1 ml. of serum. Hence, approximately one-sixth as much seed nitrogen was required for neutralization of serum reagins as for the precipitation of symptoms by the oral route.

As anticipated, the strength of extract needed for a positive scratch-test proved to be relatively great in comparison with any other tissue test. Exract containing about 1/50 the ingestion dose produced the threshold response in duV.

In the case of the other three patients, differences of a comparable order of magnitude were found to exist between the clinical and the other provocative doses. This will be made clear by the over-all ranges listed at the bottom of Table II. These ratios of comparison between ingestive and other thresholds show that the passive-transfer neutralization requirement was relatively great, from six to 300 ingestion doses being required to exhaust 1 ml. of serum. The ratios were larger for the other tests in the following order: the scratch test, the indirect skin test (Prausnitz-Kustner), the conjunctival, and finally the intracutaneous method. It was sur-

TABLE III. ESTIMATE OF MAXIMAL* ALLERGEN CONTENT OF COTTONSEED OIL
By Scratch Tests with Cottonseed Extract and Washings from Oil

Name	Ingestion Dose of Extract (in PNU)	Scratch Test Dose with Extract (in PNU/ml)	Extent of Concentration by Washing	Estimated Allergen Content of Oil (in PNU/ml)	Estimate of Volume of Oil Containing Ingestive Dose (in liters)
duV	128	2.5	60-fold	<0.04**	>3.2†
Sen	2,000	1.0	10-fold	<0.1	>20.0
Woo	1,000	5.0	60-fold	<0.08	>12.5
Sac	10,000	50.0	60-fold	<0.8	>12.5

*All scratch-tests with the oil and its washings were negative.
**The figure obtained when the scratch-test dose with extract was divided by concentration of washing.
†The figure obtained when the above result was divided into the ingestion dose determined for the patient. Example: $\frac{2.5}{60}$ = .04 units of N; 128 ÷ .04 = 3,200 ml. of oil.

prising to learn in this way that millions to billions of times more nitrogen was tolerated by the oral route than by the cndermal test.

Having determined the concentration of allergen required for the minimal scratch-test response, we were in a position to evaluate any activity in the seed oil. However, no positive responses could be elicited by scratch-testing with the latter, so that it became necessary to concentrate its water-soluble contaminant by means of small, saline washings. Such washings likewise failed to elicit more than suggestive erythemas. One was forced to conclude, therefore, that any active allergen remaining in the oil was present in amounts so small as to have no practical significance for the allergic consumer. The theoretical volume that could be tolerated orally by our patients was roughly estimated for the oil as follows:

The first patient gave no response to scratch-test with a washing obtained from 60 volumes of oil (Table III). This negative result indicated that fewer than 2.5 P.N. units per ml. must have been involved, since she had been found capable of reacting to seed extract in this concentration. Assuming that thorough shaking had removed all the water-soluble activity from the oil, there must have been fewer than 0.04 units per ml. in the unwashed oil (1/60 of 2.5 units). Carrying such calculations further, it was estimated that the patient could consume at least 3.2 liters of oil without obtaining enough of the water-soluble allergen to give her clinical symptoms. The figure, 3.2 liters, was obtained by dividing 128 units, her ingestive requirement, by .04 units per ml.

The second patient was found to be inordinately responsive by scratch-test as compared to ingestion. Her ingestion-scratch ratio was 2,000, whereas for the other patients this fell between 50 and 200 (Table 2). In spite of her capacity to detect minute amounts of seed by scratch-test, neither the oil nor washings prepared from 10 volumes led to any erythema in her skin. Consequently the oil was assumed to contain fewer than 0.1 unit per ml., and the conclusion was drawn that the patient could ingest 20,000 ml. of oil before approaching her clinical provocative dose of 2000 units of seed nitrogen.

The theoretical tolerances of the other two patients for ingested oil were

also outside the realm of practical significance. It was not surprising, therefore, that the earlier oil-ingestion experiments resulted negatively, as cited below.

With one exception, the ingestion of U.S.P. cottonseed oil in amounts up to 30 ml. caused no symptoms of any sort. The exception was encountered in Sen who was revolted by the taste of the oil and developed mild, transient nausea after ingesting 20 ml. on two occasions. She made no complaints when given a similar meal of corn oil. The nausea was interpreted as being due to slight rancidity. It was not referable to allergy in view of the patient's history that her sole clinical response to cottonseed allergens was bronchial, regardless of whether it was contacted by inhalation or by ingestion.

No effect was noted in the remainder of the group after ingesting the following volumes of U. S. P. cottonseed oil: duV, 2 ml.; Woo, 20 ml., and Sac, 30 ml. In view of the high ingestion thresholds determined for the water-soluble constituents of cottonseed and in face of the low nitrogen content of the oil, it would have been safe to have offered much larger measures of oil for these ingestion studies, and even to have tested concentrated washings in large volumes by the oral technique. It is hoped to do so in the future.

DISCUSSION

Although tests of the skin are of value for screening purposes, it has always appealed to the author that the ultimate diagnostic procedure for allergic cases should be applied to the organ involved in the clinical complaint, such as the nose or the eye of the hay fever patient, the bronchial mucosa of the asthmatic, the gastrointestinal tract of the food-sensitive individual. Tests of the skin seem especially undependable in the case of food allergy because the results so seldom parallel the clinical complaint, misleading one by false positive as well as by false negative findings. This unreliability has no doubt been responsible for the optimistic claims made for such procedures as the leukopenic index.

Although some food allergists have recently veered away from cutaneous techniques and are resorting to ingestion tests, they have failed to make adequate distinction between allergenic and psychogenic results. Furthermore, little or no attempt has been made to appraise the degree, or threshold, of sensitization by means of ingestion studies.

In the present study, the author has aimed to overcome these two shortcomings of the otherwise promising ingestion test by (1) conducting all feeding experiments in a masked manner so as to control psychic factors, and (2) by using measured amounts through the feeding of standardized extracts in increasing doses at half-hour intervals until allergic symptoms develop. These principles have been recently applied to corn allergy in the form of standardized test puddings, carrying labels which could not be decoded by the physician or his patient until the entire experiment, with

control as well as allergenic meals, had been concluded. The results will soon be published.

By resorting to extract rather than food, we have been able to use as a test meal the same extracts as those employed for concurrent threshold tests of the skin, eye and serum-sensitized site. In time, such parallel studies should permit a statistical evaluation to be made of the various tissue tests in terms of the clinical or ingestive test. Eventually, one should be able to eliminate the more complicated ingestion procedure. By applying an ingestive index to the value determined by one of the tissue tests, one should be able to calculate what the approximate clinical tolerance would be. This diagnostic short cut could only be used, of course, with those allergens which produce reliable cutaneous and/or conjunctival reactions. Cottonseed falls in this class. For less dependable foods, the ingestion test would probably have to remain the guide to sensitivity.

The figures given in the tables of this article are based on approximate endpoints and a limited number of patients. They are the outcome of pilot experiments which aimed to determine differences in the order of magnitude between ingestive and tissue tolerances and to work out a new, more objective approach to the diagnosis of food allergy. They also describe a means of appraising roughly the clinical significance of any contaminating allergen in edible oils. It is hoped that similar studies will be instituted by others so that the clinical significance of various tissue tests may eventually be expressed as an index.

CONCLUSIONS

1. Through controlled conjunctival, intracutaneous and scratch tests, the minimal amounts of extract required for the allergic responses have been determined for four cottonseed-sensitive patients. The amounts needed for the Prausnitz-Kustner test and for exhaustion of serum reagins have also been estimated by means of passive transfer studies.

2. A new type of threshold ingestion test has been described which uses the same preparations of seed extract as those employed for concurrent tissue-tests.

3. Ratios calculated by comparing the results of the ingestion method with those found by tests of the other tissues reveal that hundreds to millions of times more nitrogen is required for the response to ingestion than for the first reaction of the skin, conjunctiva or serum.

4. Comparisons between the responses to extract and to saline washings of cottonseed oil indicated that little if any seed allergen remains in the oil. Indeed, liters of oil would have to be consumed even to approach the ingestive or clinical doses of any of our patients.

5. It is hoped that the general principles outlined for the more scientific

(Continued on Page 125)

COTTONSEED PROTEIN vs. COTTONSEED OIL SENSITIVITY

V. Cottonseed Asthma: Protein vs. Oil

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BECAUSE sensitivity to the protein fraction of cottonseed is often of high degree, allergists have advised avoidance of dust from mattresses and furniture stuffed with cotton linters, foods containing cottonseed flour, and cottonseed oils used in salad dressing, vegetable shortening and oleomargarine. Theoretically there is no reason to anticipate that sensitivity to the water-soluble cottonseed protein would indicate associated sensitivity to the oil. However, it has been assumed that the refined oil might contain traces of protein sufficient to produce symptoms.

Most authors of books on allergy published between 1931 and 1939, by inference or by direct statement, indicate that the oil should be avoided. In 1940, Bernton, Spies, and Stevens,[2] in their study of five cases highly sensitive to cottonseed protein, concluded that "Patients who are sensitive to the water-soluble cottonseed extractives may safely be spared the inconvenience of attempting to avoid foods containing cottonseed oil." This research gave the writer courage to discontinue advising cottonseed protein-sensitive patients to avoid cottonseed oil products. Later, clinical tests were made using the oil in tablespoonful doses orally, followed by 1 c.c. doses intramuscularly. No local or constitutional reactions resulted, and it was assumed that the problem was solved.

However, since 1940, at least eight books on allergy have reiterated the warning that clinical symptoms could and often did follow ingestion of the oil. The most lenient attitude was expressed by Unger[7] in 1945 when he stated, "There is some doubt as to the allergenic role of foods . . . which contain cottonseed oil; until this is cleared up, such foods should be avoided." At the other extreme, Rowe[5] writes, "Sensitization to cottonseed allergen, especially by inhalation, may be as severe as any encountered. Such patients usually cannot take any cottonseed oil or fat by mouth without severe symptoms." In 1945, Criep,[3] also discussing cottonseed sensitivity, stated, "There is serious doubt as to whether the ingestion of cottonseed oil may give rise to allergic symptoms, although this is probable in patients who are extremely sensitive to cottonseed. In these instances the sensitivity must be to a water-soluble fraction of cottonseed." No clear statement could be found in the literature except that of Bernton, Spies and Stevens which unequivocally removed the suspicion that ingestion of cottonseed oil would be harmful to cottonseed protein-sensitive patients.

The question of the antigenicity of vegetable oils arose again late in 1947

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TABLE I. COTTONSEED ASTHMA: PROTEIN VS. OIL

Case No.	1	2	3	4	5	6	7	8	9	10	11
Sex	M	M	M	M	M	M	M	F	F	M	F
Age of onset (in years)	3	¼	2	2½	1½	1	18	16	8	31	½
Age came for treatment	6	10	5½	9	3½	13	24	18	21	33	31
Age December 31, 1948	21	24	18	21	13	21	31	22	22	34	32
Years observed	15	14	12	12	10	8	7	4	1	1	⅔
HISTORY OF SYMPTOMS FROM CERTAIN BRANDS OF:											
fig newtons	+	+	+*	+		+	+	+		+	
cookies	+	+		+	+	+	+	+		+	
cup cakes	+	+		+	+	+	+			+	
graham crackers	+				+	+		+		+	
health bread											+*
candy bars	+			+	+		+				
"cake" doughnuts	+*	+*		+	+	+	+		+	+	
"raised" doughnuts	o	o	o	o	o	o	o	o	o	o	o
salad oils	o	o	o	o	o	o	o	o	o	o	o
vegetable margarine	o	o	o	o	o	o	o	o	o	o	o
oleomargarine	o	o	o	o	o	o	o	o	o	o	o
Serology	o	o	o	o		4+	o		o	o	o
Passive Transfer	+	+	+	+		o	o		+	+	o
PROTEIN FRACTION											
Prick tests											
Cottonseed 1%	4+	4+	4+	6+	4+	4+	4+	2+	4+	4+	8+
CS-1A**	6+	10+	4+	10+	4+	6+	4+	3+	6+	6+	10+
Conjunctival tests											
Cottonseed 0.1%	4+	4+	2+	4+	2+	o	2+	2+	2+	2+	4+
Immunizing injections	+*	+*	+	+*	+	+	+*	+	+	+*	
TESTS WITH COTTONSEED OIL											
Skin (prick method)	o	o	o	o	o	o	o	o	o	o	o
Conjunctival	o	o	o	o	o	o	o	o	o	o	o
Nasal	o	o	o	o	o	o	o	o	o	o	o
Oral	o	o	o	o	o	o	o	o	o	o	o
Ingestion 15 c.c.	o	o	o	o	o	o	o	o	o	o	o
Inhalation	o	o	o	o	o	o	o	o	o	o	o
Injection 1.0 c.c. (I.M.)	o	o	o	o	o	o	o	o	o	o	o

Unfilled spaces indicate test was not made.
*Indicates constitutional reaction.
**CS-1A, a highly purified cottonseed protein fraction obtained from Henry Stevens, Ph. D., Head, Allergen Research Division, United States Department of Agriculture.

when hearings of the Federal Security Agency were held and leading allergists were asked to testify. The testimony of G. T. Brown and McGrath indicated that from their clinical experience many patients sensitive to cottonseed protein also developed symptoms when the oil was ingested. A contrary opinion was given by Bernton, Mitchell, Figley, and Loveless. None of these latter witnesses had observed a cottonseed protein-sensitive patient in whom it could be conclusively demonstrated that the oil was capable of producing allergic symptoms. A verbatim record of the testimony taken at these hearings has been recently published.[1] Figley,[4] in his presidential address before the American Academy of Allergy, presented the present status of the problem, summarizing the testimony given in the hearings, and gave a detailed description of the oil refining process.

The object of this communication is to present the writer's experience in this controversial area.

Of 906 nonseasonal extrinsic asthmatics, thirty-seven (4 per cent) gave positive skin reactions to cottonseed protein by the scratch or prick method.

Table I summarizes the results in a study of eleven highly sensitive cases,

eight males and three females, observed from eight months to fifteen years. The age of onset of asthma was before three years in seven cases. All had experienced severe asthma following exposure to cottonseed protein by inhalation, ingestion, or injection. The history indicated that the eating of certain brands of fig newtons, cookies, cup cakes, graham crackers, health breads, "cake" doughnuts, and candy bars was followed within a few minutes by one or more of the following symptoms: tingling and edema in the mouth and tongue; nausea, vomiting, and abdominal cramps; generalized itching and urticaria; and asthma. "Raised" doughnuts and edible cottonseed oils could be eaten with impunity.

Prick tests on the upper back, with cottonseed protein (Arlington) and CS-1A,[6] 1 per cent in glycero-saline, gave consistently positive reactions, generally larger wheals being obtained from the latter extract.

Conjunctival tests with cottonseed protein (Arlington) 0.1 per cent in saline were positive in all except Case 6. Subsequently, he experienced a sharp attack of asthma following the inhalation of a small quantity of powdered antigen.

Passive transfer tests were positive to cottonseed protein in six, negative in three, and not done in two instances.

Specific immunizing injections up to .5 c.c. of 1:1,000 dilution had been given to all but Case 11, and constitutional reactions were encountered in five.

In sharp contrast were the results of experiments with undiluted cottonseed oil (Wesson oil, purchased at a local grocery) which was instilled into the conjunctival sac, dropped into the nose, inhaled in nebulized form, ingested in 15 c.c. amounts and injected intramuscularly in doses of 1 c.c., without producing any local or constitutional reactions. Prick tests on the upper back were also negative.

These experiments indicate that edible cottonseed oil lacks the capacity to produce allergic symptoms, even by intramuscular injection, in patients known to be highly sensitive to cottonseed protein.

SUMMARY

1. Eleven asthmatics, clinically and immunologically highly sensitive to cottonseed protein, were exposed to edible cottonseed oil by skin tests, mucous membrane tests, inhalation, ingestion, and intramuscular injection without local or constitutional reactions.

2. These experiments confirm the opinion of Bernton, Spies, and Stevens and provide additional evidence that sensitivity to cottonseed protein does not indicate concomitant sensitivity to cottonseed oil.

3. In view of the above findings it seems unnecessary to advise patients sensitive to cottonseed protein to avoid foods containing cottonseed oil.

(Continued on Page 89)

IDIOBLAPTIC ALLERGY AS AN IMPLEMENTING BACKGROUND FACTOR IN ANTERIOR POLIOMYELITIS

An Exploratory Study

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and
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THE roots of this investigation reach back to the finding by Boone, Chase, and Brink,[1] that bacteria not normally invasive from the intestine become invasive during anaphylactic shock. The ability of shock to open the doorway to invasion by latent and low-grade infection has been further investigated by Weisberger,[12] Burn, Chandler and Hartshorn,[4] and others, and discussed by Locke[8] and by Good and Campbell,[7] who were able to implement the precipitation of a latent viral herpetic infection, in the rabbit, by means of induced anaphylactic shock.

The diagnostic criterion of the presence of the reaction to ingested food that has been described by Coca as *idioblapsis* is a rise in pulse rate so far exceeding that produced by the ingestion of foods which do not cause that disturbance as to suggest the production of a shock-like reaction in the areas most affected.

Coca had found an association between freedom from idioblaptic allergy and freedom from common cold. In a group carefully screened for presence of the revealing, excessive pulse rise following ingestion, and free also of a series of associated symptoms (headache, et cetera) which had been found by him to occur so commonly during the reaction phase of idioblaptic allergy as to have value as accessory indications, about 8 per cent were found who had no recognized signs of the presence of idioblaptic allergy. Of this 8 per cent, none was subject to common cold. Conversely, in the total of fifty-two persons in the group who appeared to be cold-free, only fifteen appeared to have any allergic symptoms. The symptoms occurred, in these fifteen, rarely, or occasionally, or "at the menstrual period," or "formerly," or only from a certain food which the individual had learned

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From the Sister Elizabeth Kenny Foundation, Minneapolis, Minnesota.
After this investigation had been concluded, the voluminous records analyzed and the results tabulated for publication by Doctor Locke, he suffered a severe illness which has prevented him from preparing the usual explanatory report. Doctor Locke had all the material sent to Dr. Arthur F. Coca with a request that he undertake the writing for him. Doctor Locke has read and corrected the manuscript, and fully approves its factual content.
Two circumstances greatly influenced the launching and conduct of this investigation. The first of these was the active interest of Dr. Fred W. Wittich. Dr. Wittich placed the plan before Mr. Marvin L. Kline, director of the Sister Elizabeth Kenny Foundation in Minneapolis, offering his service in furthering the work; and he was successful in obtaining the Foundation's approval and financial support of the undertaking. The second important circumstance was the enlistment, as investigator, of Donna B. Baughman. Mrs. Baughman was specially trained in the procedure, and was at home in Minneapolis where the study was made. Every courtesy and facility was given her at the Foundation, including office accommodation for the interviews. Dr. John F. Pohl was especially helpful in the arrangements for comprehensive interview and inquiry into family background, as was Dr. S. R. Seljeskog in making available the extensive files of the Sister Kenny Institute. The "control" group were students at the Southwest High School of Minneapolis, who were made available for study through the co-operation of Dr. Alice Hartig, medical director of the Minneapolis Public School System. It is a pleasure to acknowledge the interested co-operation of Dr. Samuel I. Hicks, superintendent of the Pearl River school, in the control survey for that locality reported in Tables I and III.
Doctor Coca is an Honorary Fellow of the American College of Allergists.

to avoid. Thus the cold-free individuals were those either altogether free from idioblaptic allergy or those with an allergy classifiable as mild or well controlled. Several of the group who previously had been frequently subject to common cold became cold-free following identification and elimination of food allergens from the food intake.[5]

Locke, in a study made in collaboration with Brown and associates at Stephens College, found a quantitative association between number of symptoms pointing toward presence of idioblaptic allergy and number of colds developed. Students found at the beginning of the school year to have a total of zero to one indication of presence of allergy developed during the subsequent year an average of 0.94 $\pm$ .08 colds, as contrasted with the average of 3.41 $\pm$ .29 colds for the students found at the beginning of the year to have a total of more than nine indications of presence of allergy.[3] A related approach was used in his analysis of the data collected in this investigation of background factors in poliomyelitis.

The idea that idioblaptic allergy may predispose to poliomyelitis was suggested by a report that about 90 per cent of adults examined carry in their blood antipolio protective antibodies. These figures suggest that about 10 per cent of the population may be naturally resistant to the virus of poliomyelitis, which therefore does not gain immunologically effective entrance. This percentage is close to that which has been found for persons appearing to be naturally resistant to the common cold (near 10 per cent, according to Paul and Freese[10]; near 12 per cent, according to Brown[2]; near 12 per cent, according to Locke[9]; and near 12 per cent, according to Coca.[6]

The "low-grade" infective power of the polio virus in the sense of Locke is indicated by the fact that only a small percentage of infected persons develop a clinically recognizable case of polio,[11] and of these about 75 per cent recover without residual disability.

The following differences exist between the common cold and poliomyelitis as subjects for an investigation of this type:

1. It is easy to identify the cold-resistant person by mere questioning; whereas one can identify the persons that presumably are naturally resistant to poliomyelitis only through the questionable negative finding in an examination of the blood for polio-protective antibodies.

2. It is likewise easy to identify cold-susceptible persons; whereas most polio-susceptible persons that actually become infected present no characteristic symptoms of the disease at any time.

3. Infection with the cold virus is indefinitely recurrent due to the short term of the acquired immunity; and this circumstance permits the observation of any resistance to that infection which may at any time be experimentally induced.

4. On the other hand, a person's first effective exposure to the virus of poliomyelitis results in an infection, with or without noticeable symptoms,

TABLE I.

Frequency with which hives, heartburn, etc. were reported as a recurring experience by the persons questioned in the contrasted control and polio groups.

Symptom weight (as an indication of tendency to food allergic reaction)	Percentages subject to Hives, Heartburn, etc.					
	Control Group			Polio Group		
	Male	Female	Combined	Male	Female	Combined
(1) Hives	16	20	18	13	27	19
(0) Heartburn	19	10	15	14	13	14
(1) Canker Sores	60	64	62	54	63	58
(1) Constipation	4	9	6	20	35	27
(1) Rhinitis	17	21	19	27	29	28
(1) Nervousness	6	11	8	8	21	13
(0) Stammering	10	4	7	9	6	8
(0) Enuresis	7	7	7	28	16	23
(0) Asthma	10	4	7	1	7	4
(1) Headaches	29	23	26	43	34	38
(1) Indigestion	30	30	30	32	41	36
(1) Tiredness	5	12	8	15	21	18
(1) Dizziness	29	23	26	14	25	19
(0) Hemorrhoids	0	0	0	4	6	4
(1) Neuralgia	15	21	18	33	33	33
(0) Hay Fever	25	14	19	5	9	7
(0) More than two colds per year	47	43	45	58	56	57
(0) % with **not** more than 1 cold per year and no rhinitis			17			9
(2) Pulse above 84	11	16	13	30	33	31
Total Number	126	120	246	142	107	249

	Control Parent Group (137)	Polio Parent Group (399)
(1) Parent with a total symptom weight of 2 or more*	64	90
Percentages of the control and polio groups with a total symptom weight of 2 or more*	71	100
Pearl River Students	67	

*Maximum pulse above 88 in pulse range test, or pulse range exceeding 14, also given a weight of 2 in the absence of pulse above 84—for the computation of total weight only.

which is regularly followed by the production of a lasting immunity. Hence any attempt to establish a resistance to the virus of poliomyelitis must be made in advance of the individual's first exposure, and the efficacy of the procedure has to be evaluated through statistical analysis.

Notwithstanding these several relative handicaps, and the further limitation that no "control" group was available that consisted of more than a small fraction of actually polio-resistant persons,* the investigation was begun on August 1, 1948, and continued to February 1,1949.

Two groups of individuals were examined for the symptoms and signs of idioblaptic allergy that are listed in Table I. One group consisted altogether of known victims of poliomyelitis; and the other ("control" group) consisted entirely of boys and girls, of age thirteen to nineteen, with no characteristic symptoms of infantile paralysis at any time in their lives and with no close relative who had ever developed infantile paralysis.

The procedure was modified from that used by Locke in the Stephens College study in the addition to the list of conditions on which information

*A large part of the population is not *resistant* to polio but *immune* to it as a result of a presumptive immunizing but nonparalytic attack. The naturally resistant individual differs from the immune individual in that his protection derives from an absence of factors predisposing to infection rather than to a presence of immune antibodies produced following an earlier attack.

TABLE II. PERCENTAGES FOR THE POLIO SERIES EXAMINED WITH RESPECT TO AGE GROUPINGS

Age	3-7	8-12	13-19	20-45	Combined
Total number	68	80	69	32	249
Hives	16	14	22	31	19
Heartburn	3	6	16	50	14
Canker sores	42	65	58	72	58
Constipation	28	26	17	44	27
Rhinitis	18	29	32	41	28
Nervousness	9	13	12	28	13
Stammering	7	10	7	3	8
Enuresis	26	25	17	22	23
Asthma	4	1	6	3	4
Headaches	26	36	42	56	38
Indigestion	26	43	32	50	36
Tiredness	13	15	20	31	18
Dizziness	1	19	22	50	19
Hemorrhoids	0	1	1	28	4
Neuralgia	24	36	35	41	33
Hay fever	1	4	14	9	7
Pulse above 84	36	30	25	36	31
More than two colds per year	69	56	48	53	57

was sought, of several conditions which had since been observed as accompaniments of idioblaptic allergy. These were enuresis (proved allergic in one case by its complete absence for one and one-half months during avoidance of the few pulse-accelerating foods and its prompt recurrence when these foods were returned to the diet), stammering, and hemorrhoids (similarly proved allergic). Among these three, only the data concerning enuresis provided a significant percentile difference in its occurrence in the polio and the control groups.

Mrs. Baughman questioned her subjects and their parents carefully, and the symptoms recorded were those appearing to recur in cause and effect relationship with a food source and, in the polio series, *previous* to the poliomyelitis attack.

Blood pressures were noted in some of the parents without any useful differentiating conclusions being derived from those data.

The occurrence of hay fever and bronchial asthma was noted, although the former purely reaginic, atopic manifestation does not come into consideration in the present problem. The lower incidence of hay fever among the polio group is due to the relatively younger ages of most of the individuals in that group as compared with the high school student controls.

Incidentally this difference in the ages of the two groups makes the markedly higher incidence of some allergic symptoms among the younger polio group the more significant of their predisposing influence, since the incidence of all those symptoms, excepting enuresis, tends to increase with age. It seems of possible special interest, pending confirmation, that the incidence of neuralgia among the polio group was even higher among the polio group of ages eight to nineteen (35.5 per cent) than it has been found by me in fifty-four allergic adults (27.8 per cent).

A general summary of the quantitative findings of this investigation, as collected and classified by Locke, is presented in Table I.

TABLE III.

Showing marked difference in the incidence of seven allergic manifestations among the polio cases and the controls.

Symptom	Polio cases (249) per cent	Controls	
		Minneapolis (246) per cent	Pearl River (269) per cent
Enuresis	23	7	7
Constipation	27	6	12
Abnormal tiredness	18	8	9
Pulse over 84	31	13	—
Rhinitis	28	19	14
Neuralgia	33	18	15
Headaches	38	26	20

In Table II the data from the "polio group" are reclassified according to the ages of the individuals.

In Table I it is seen that the incidence of some symptoms, for example, hives, heartburn and canker sores, is approximately the same in both groups. However, the incidence of other symptoms is markedly different in the two groups, and it is *always greater* in the polio group. The symptoms whose incidence differed widely in the two groups are listed in Table III. Included in the table are the corresponding figures obtained in a similar survey which I carried out in the winter 1948-9 among the high school students in Pearl River, who constitute a convenient second control group.

Another marked quantitative difference in the polio and control groups seems significant. In Minneapolis, it was found that *all* victims of polio presented two or more symptoms by "weight"† of food allergy whereas 29 per cent of the control group showed either no allergic symptoms or only one symptom. Among the students in the Pearl River High School 33 per cent reported fewer than two symptoms—confirming Locke's result. This difference was found in Minneapolis to extend into the families. Ninety per cent of the polio-parent group had more than two symptoms against only 64 per cent for the control-parent group.

DISCUSSION

These consistently wide differences, especially when they are considered in the light of the comparable studies of the relationship of idioblaptic allergy to susceptibility to common cold, suggest that children born free from idioblaptic allergy or rendered free from its hazard through identification and avoidance of all pulse-accelerating allergens[6] may be either quite resistant to the virus of poliomyelitis or at least safe from the serious consequences of that infection.

The results of this study suggest four categories of the population with

†The "weight" of indication of the presence of idioblaptic allergy increases with the number of symptoms reported which are known to be commonly associated with that condition. Pulse above 84 and/or a maximal pulse above 88 in a pulse-range test, or pulse range exceeding 14, were given a weight of 2 since these indications have been found to point unquestionably toward presence of idioblaptic allergy.[6] Weights of 1 were assigned to the findings in Table I which have been found to be suggestive of the presence of idioblaptic allergy but not conclusive in the absence of corroboration by the objective pulse-range test.

respect to idioblaptic allergy and infantile paralysis: (1) those free from reaction to an idioblaptic allergy and therefore quite resistant to the virus, (2) those few who are markedly affected by a certain type of idioblapsis (defined for the present by the seven manifestations listed in Table III), and therefore in special danger of the serious consequences of the infection, (3) those less markedly affected by the allergic handicap and therefore able to cope with the infection without suffering recognizable damage, and (4) those immune as a result of earlier, nonparalytic exposure.

The findings also suggest study of certain appropriate therapeutic measures.

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A CLINICAL EVALUATION OF CHLORCYCLIZINE (PERAZIL)

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AN EXAMINATION of the literature on antihistaminic agents demonstrates the fact that there is, as yet, no satisfactory objective method for their clinical evaluation. The usual routine followed consists of the selection of a group of allergic patients (no two of whom are alike) to whom the drug is administered under very varied circumstances. The patient's opinion is the only actual criterion available. When lesions (such as hives) are visible, there can, of course, be no doubt as to their disappearance. When a nose is, however, considered less stenotic, or pruritus less severe, the criteria are less acceptable.

The following paper makes no new contributions as to method of study, except to list the patients as to the dosage level at which they were relieved. Their comments regarding the efficacy of the drugs they used are accepted in full. Relief is defined as complete or almost complete freedom from symptoms. Any other report is taken as subjective and listed as meaning that the ingestion of the drug was without effect. The patients presented the usual allergic syndromes observed during the tree, grass and ragweed pollen seasons of 1949 in New England. The effects of Perazil upon several miscellaneous conditions are also listed.

One observation of interest may be made at this point. The opinions of the six physicians who did the study were by no means unanimous, and the evaluation therefore concerns them as individuals, in that some (EAB and RCN) consistently achieved better results than did the others. One reported the poorest results (JPM), and the other three were consistent in the number of patients relieved and the degree of relief or side reactions. Had all six of us written individual papers, the results would have been as varied as those noted in the literature for other drugs of the same type. It would seem, therefore, that the percentile reports by individual physicians who study small groups of patients are limited in applicability and that the results achieved by a number of physicians working together with large groups of patients would result in internal checks and balances within the group and therefore reflect, perhaps, data more nearly authentic. This, again, can only be acceptable against the background of the type of patients seen, as in private practice, public clinics, or compensation clinics, the type of sensitivity and the severity of the symptoms, the season, the specific

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The material for these studies was furnished by the Burroughs Wellcome Company, Tuckahoe, New York.
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treatment given, and the general geographical location of the clinical evaluation experiment.

ANIMAL PHARMACOLOGY

Since Chlorcyclizine is a new drug, its bibliography is limited. The compound has the structural formulae N-methyl-N'-(4 Chlorobenzhydryl) piperazine. The pharmacological action in animals has been reported on by Castillo and his colleagues,[1] whose studies show that Perazil had four times greater potency than Benadryl, as tested by its effect on the histamine-induced contractions of the isolated guinea pig tracheal chain. Perazil acts more slowly than Benadryl, and its antihistaminic effect lasts longer after washing. One hour after an oral dose of 2.5 mg./kg. of Perazil, 62 per cent of thirty-seven guinea pigs are protected from nebulized 0.2 per cent histamine diphosphate, while at four- and five-hour periods, 83 per cent and 69 per cent are, respectively, protected. From a comparative point of view, Tagathen protects 63 per cent, one, four or five hours after dosing; Neo-Antergan protects 60 per cent, 40 per cent and 60 per cent, respectively, while Pyribenzamine and Thenylene are markedly less effective.

The oral administration of Perazil in doses of 10 mg./kg. prevents or reduces the severity of broncho-constriction following exposure of guinea pigs to nebulized histamine, up to twenty-three hours. An intravenous injection of 3 mg./kg. into anesthetized dogs blocks almost completely the depressor effect produced by 50 micrograms of histamine diphosphate for a period of up to two hours. The spasm produced by histamine on the isolated guinea pigs ileum is antagonized by Perazil as are the spasmogenic effects of acetylcholine and barium chloride.

When Perazil is given intravenously to dogs in doses of 3 mg./kg., the blood pressure falls 33 to 90 mm. of Hg., but in all instances returns to normal within three minutes.

The local anesthetic activity of Perazil in guinea pigs is the same as that of Benadryl when tested by the intradermal wheal method, a 1 per cent solution of each drug producing anesthesia lasting twenty-two minutes. A test of the mydriatic action on the rabbit eye shows a 1 per cent solution of Perazil as negative, while a 1 per cent solution of Benadryl produces a 20 per cent dilatation of the pupil.

The LD_{50} of Perazil in mice is 137 mg./kg., as compared to Neo-Antergan (115), Tagathen (105), Thenylene (77), Pyribenzamine (67), and Benadryl (69), respectively.

HUMAN PHARMACOLOGY

The human pharmacology was studied by Jaros and his colleagues.[2] In thirty subjects, of whom sixteen were allergic and fourteen non-allergic, fifteen were treated with 100 mg. of Pyribenzamine and fifteen with 100 mg. of Perazil. Scratch tests were performed with 1:4,000,000 to 1:512,000 histamine solutions. The patients were then reversed, those receiving

Pyribenzamine being given Perazil and vice versa. Perazil produced a greater degree of inhibition of the wheal response than did Pyribenzamine, the effects lasting about thirty-two hours longer. In one test with the 1:256,000 dilution of histamine four hours after a dose of Pyribenzamine, fourteen of fifteen patients had wheals 1 to 2 mm. in diameter, while only two of fifteen treated with Perazil had similar wheals. In a cross-over experiment, four of fifteen treated with Perazil had wheals 0.5 to 2 mm. in diameter, while thirteen of fifteen given Pyribenzamine presented wheals 0.5 to 2 mm. in diameter. Of a total of sixty-three doses of Perazil, seventeen caused drowsiness, while twenty-four of fifty-six doses of Pyribenzamine had the same reaction. The degree of drowsiness, however, was milder after Perazil than Pyribenzamine. Side reactions, which included dryness of the mouth, nausea, headache, light-headedness, nervousness and similar reactions, occurred in only twenty-one of the sixty-three patients given Perazil, and in thirty-three of the fifty-six patients given Pyribenzamine.

CLINICAL REPORT

In a later communication, Jaros[3] reported on twenty-three patients with hay fever, eight with atopic dermatitis, twenty-one with vasomotor rhinitis and six with acute urticaria. Only one patient with hay fever and three with vasomotor coryza failed to obtain excellent relief. Moderate improvement was obtained in eight of twelve patients with bronchial asthma. Of the eighty-four patients treated, those receiving hyposensitization and Perazil had the greatest degree of relief, with only four patients presenting mild side effects, the most frequently being drowsiness. All of the patients had had moderate to severe uncontrolled symptoms, despite the use of other antihistaminic agents.

HAY FEVER

In the present study there were, in all, seventy-five patients with "pure" hay fever. They are listed according to their dosage level. Seven required only one-half tablet, that is 25 mg., on arising to achieve complete control of their symptoms which were only present in the morning. Some of these patients required an additional 25 mg. when necessary. In none were there any side reactions, and in all, the good effect lasted the full twenty-four hours, excepting for occasional symptoms following exposure to pollen.

Two patients with uncomplicated hay fever required either 25 or 50 mg. for complete relief of their symptoms. In one of these there was moderate drowsiness. This same patient suffered from severe drowsiness with fair relief from Pyribenzamine. He could, however, take Trimeton with no drowsiness and equally good effect.

Three patients with hay fever discovered that they achieved excellent results when they took 25 mg. twice daily, making a total intake of 50 mg.

One of these complained of slight, questionable light-headedness. Neither of the other two presented side reactions. One of these patients achieved equally good results with Pyribenzamine and Trimeton, although he stated that the effect of Perazil was longer than that of any of the other antihistaminic agents he had taken. One additional patient required 25 mg. three times daily, with complete relief and no side reactions.

There were eighteen patients who took a single tablet of 50 mg. when necessary for complete relief in all and no side reactions. One of these patients had little relief with Decapryn, better with Trimeton, and excellent with Perazil. Another reported moderate relief with Pyribenzamine and excellent with Perazil, and a third achieved good relief with Trimeton but better with Perazil. One reported wakefulness from Trimeton, although the therapeutic effects were excellent. Perazil gave an equal degree of relief with no wakefulness.

Thirty-six patients of this group suffering from hay fever took 50 mg. twice daily. Fourteen of these had never had any other antihistaminic drug. They achieved complete relief with no side reactions. One of these reported moderate relief with Pyribenzamine, which, however, caused drowsiness. Another patient had extreme drowsiness with both Pyribenzamine and Benadryl, with no side reactions from Perazil. Two others, who had had complete relief with Perazil, with no side reactions, achieved equally good relief with Pyribenzamine and Benadryl, which, however, did not last as long. Two patients who reported complete relief with Perazil had such drowsiness with Benadryl that they could not continue their work. They also achieved moderate benefit with moderate drowsiness from Pyribenzamine. One patient had equally good results from Perazil and Trimeton, with no side reactions from either. This same patient was not benefited from Pyribenzamine and had drowsiness with Benadryl. One patient found Trimeton and Perazil of equal value. This same patient had complete relief with no drowsiness with 25 mg. doses of Benadryl, and complete relief and moderate drowsiness with 50 mg. of the same drug.

In the comparative studies done with patients with hay fever who took 50 mg. of Perazil twice daily, one, who achieved complete relief in forty-eight hours, stated that Perazil lasted longer although it gave equally good relief as compared to Pyribenzamine. Another patient discovered that he had required four doses of other antihistaminic agents, including Benadryl and Pyribenzamine, but only two doses in twenty-four hours when he took Perazil. He suffered from no side reactions. One patient stated that Pyribenzamine and Perazil worked equally well, except that the former caused slight drowsiness, the latter causing no side reactions. One patient, who had excellent relief with Trimeton, said that he had equally good but longer-lasting effects with Perazil. One patient, with no relief from Pyribenzamine and fair relief at night with drowsiness from Trimeton, had complete cessation of symptoms and no side reactions with Perazil. Two other patients found Trimeton and Perazil equally good with no side re-

actions and complete cessation of symptoms. One patient, who achieved complete relief with no side reactions from Trimeton and Perazil, stated, however, that he preferred Trimeton.

The side reactions require some note. There were, in all, five patients in whom they occurred. In one, they were of moderate degree and consisted of drowsiness, shakiness and palpitations, although relief of allergic symptoms was complete. One patient, who had extreme drowsiness with Pyribenzamine, had slight drowsiness with Perazil. One patient with moderate drowsiness, nausea and light-headedness preferred Pyribenzamine. Repeat doses of Perazil brought on the same side reactions. One individual who had slight nausea for the first three hours after he took Perazil was thereafter able to take it without ill effect. This same patient received no benefit from Pyribenzamine. One patient had slight drowsiness with 50 mg. twice daily but could tell no difference between Pyribenzamine and Perazil, both working fairly well for moderate symptoms but neither having any effect when the hay fever was severe.

Some patients with hay fever required larger doses. One with a great sensitivity to ragweed required 50 mg. of Perazil three times daily with no ill effects and with excellent relief, and one patient required 200 mg., that is, four doses in every twenty-four hours, to achieve complete relief, the side reactions being slight drowsiness. One patient, who took one tablet on arising and retiring with complete relief, with an additional 50 mg. before exposure, had severe drowsiness with 150 mg. dosage level in twenty-four hours but no drowsiness when he reduced the dose to 100 mg.

VASOMOTOR CORYZA

There were, in all, seven patients who suffered from severe, typical vasomotor coryza associated with pale, boggy membranes in the absence of any signs of infection or allergy. Of these, one was completely relieved by 25 mg. taken when necessary and one by 50 mg. for occasional symptoms. One patient required 50 mg. twice daily, on arising and retiring, and a third required 50 mg. three times daily, with complete relief, none showing side reactions. The third patient, however, used nasal Antistine for occasional severe attacks. One patient in this group took 25 mg. when necessary, with improvement, excepting for side reactions of slight drowsiness, dryness of the mouth, light-headedness, and difficulty in walking. This patient claimed, however, that greater side reactions followed the use of Perazil than the use of Pyribenzamine, Trimeton, Benadryl and Ephedrine, although all gave equally good results. One patient, whose nose had never previously cleared with any medication, antihistaminic or otherwise, achieved complete relief with 50 mg. twice daily, and after two months, improved to the extent that she required only 50 mg. once daily. For a severe attack, however, the patient took three 50 mg. tablets in two hours, with complete relief and no side reactions. The last patient in this group achieved good

results with Perazil but required Antistine nasal solution as an auxiliary medication, there being, however, no side reactions.

URTICARIA

In all, there were fifteen patients with urticaria. Of these, one required 25 mg. twice daily for complete remission of her hives, as well as for her daily headaches. This same patient had had the unusual side reaction of swelling of the ankles following small doses of Benadryl, and stomachache following Histadyl. Seven patients required 100 mg. daily in two doses, with complete relief and no side reactions, although one of these patients had had Pyribenzamine, Trimeton, Benadryl, Vitamin K and calcium lactate with no effect, while another had had Benadryl, Pyribenzamine, with little relief and drowsiness from these and other medications. One patient had used Pyribenzamine and Trimeton with no marked, but perhaps slight, relief, with Perazil giving complete relief for twelve to twenty-four hours. Two patients required 50 mg. three times daily, with complete relief and no side reactions. Of these, one achieved some relief with Pyribenzamine and Chlor-Trimeton, for periods up to five hours, Pyribenzamine causing slight drowsiness. In this same patient, Perazil gave relief lasting up to twelve hours. Another patient in this group had had Dramamine, which caused dizziness with the hives being worse, and Histadyl with no effect. Perazil completely controlled both conditions.

One patient took 50 mg. four times daily, with complete relief and no side reactions. This same patient had responded to Pyribenzamine, Trimeton, Chlor-Trimeton and Benadryl with slight benefit and mild drowsiness.

In this same group of patients with urticaria, there was one whose hives were associated with serum disease. He required Perazil in the 50 mg. dose every four hours, for six doses daily, with complete relief. There were no side reactions. One patient in this group took 50 mg. three to six times daily with improvement of her urticaria, but nevertheless complained of drowsiness, dryness of the mouth, nausea, light-headedness, and shakiness. She found relief with Trimeton taken during the day and Benadryl at bedtime until it was discovered that she was sensitive to chocolate, following the elimination of which she was completely well.

BRONCHIAL ASTHMA ASSOCIATED WITH INFECTION

Although antihistaminic agents have been of little use in infectious bronchial asthma or in severe allergic atopic bronchial asthma, except perhaps given intravenously, the drug was used in a group of typical intrinsic emphysematous patients, many of them suffering from nasal and sinus infection, as well as subacute bronchial infection. One of these seven was a child of six, who wheezed only with colds and was able to take 25 mg. with excellent results. One patient, whose asthma was extremely severe, was relieved of her wheezing while sitting still following a dose of 50 mg.

She otherwise continued to wheeze moderately, although inactive. There were no side reactions in either of the patients. A third patient took 50 mg. twice daily, with mild side reactions and no relief. She claimed some relief with Perazil but insisted on the frequent use of nebulized epinephrine (1:100) and therefore cannot be used for classification purposes. Two patients took 50 mg. five times daily with no side reactions and no effects. One patient was improved on 50 mg. three times daily, claiming as good results as with Luasmin capsules, but not as good as with epinephrine (1:100) by nebulizer. The last patient in this group took 200 mg. daily, with some relief of his nasal stenosis but no effect on his cough or wheeze.

ATOPIC ECZEMA

Of the eight patients with atopic eczema, one achieved complete relief of pruritus with 25 mg. twice daily. Another required 25 mg. three times daily, with Trimeton ointment used locally. A third patient required 50 mg. twice daily, and another, 50 mg. three times daily, none of these patients presenting any side reactions. One patient used 50 to 100 mg. twice daily with no side reactions and complete relief of pruritus. Three others required 50 mg. twice daily. One of these patients also used tablets of calcium lactate, 15 gr. by mouth three times daily, and Trimeton ointment. One, although complaining of no side reactions, preferred Trimeton.

The effect of any antihistaminic is difficult to evaluate in the group of patients suffering from atopic eczema, because of the fact that almost all of them demand, if they do not require, topical applications. In all cases, therefore, the good effect must be ascribed to both methods of treatment.

In two patients in this group, who suffered both from a residual, chronic atopic eczema and a hay fever, the eczema causing little difficulty, 50 mg. of Perazil controlled both the pruritus of the lichenified areas, and the allergic coryza to perfection. There were no side reactions on 50 mg. taken when necessary.

VERNAL CONJUNCTIVITIS

The drug was used on two patients with vernal conjunctivitis; one who had received no previous relief with Benadryl and only slight help from Pyribenzamine, but marked relief from epinephrine drops lasting two hours, achieved twelve hours of relief with 50 mg. Perazil given twice daily. A second took 25 mg. twice daily, with marked relief of the ocular pruritus but little or no effect upon the conjunctival injection. Neither patient showed any side reactions.

MISCELLANEOUS CONDITIONS

Among the miscellaneous conditions treated were dermatitis herpetiformis, psoriasis, and generalized pruritus. The first patient took 50 mg. three times daily, with no side reactions and complete relief while on the medication. One patient with psoriasis, who had taken a sulfonamide and

responded with a dermatitis medicamentosa which covered the entire body, found that Perazil gave him four to six hours' relief during waking hours. Additional medication in the form of Ipral aspirin was required for sleep at bedtime. A second patient, who complained of pruritus with psoriasis, was also relieved for a period of two weeks while using local therapy which did not affect the psoriatic lesion.

An eighty-year-old woman suffering from a generalized pruritus of the senile type achieved no relief with Perazil, having taken all other antihistaminics with no effect. One more patient with bronchial asthma and urticaria, the former being continuous and the latter occasional, had complete relief of both with 50 mg. taken twice daily, there being no side reactions.

CONTACT DERMATITIS

In contact dermatitis, we had a syndrome in which it was easy to observe the results. In all, there were fourteen patients. Of these, five took 50 mg. twice daily, and one 50 mg. three times daily, and one 50 mg. four times daily, with no side reactions and complete relief. These patients required no topical applications, excepting for the last, who used Lassar's paste. Of the remaining patients, two took 50 mg. twice daily with complete relief of symptoms and no side reactions, using Pyribenzamine cream locally. Another took 50 mg. three times daily, with little relief, the patient claiming that Trimeton and Benadryl helped to a much greater extent, there being no side reactions to any of the three drugs. One other patient took 50 mg. twice daily, using Lassar's paste locally, which did not affect the pruritus when used alone. Two patients took 50 mg. daily, using Trimeton ointment locally, and one took 50 mg. twice daily with only partial control of the pruritus, achieving better results with Trimeton tablets and ointment.

BRONCHIAL ASTHMA DUE TO FOODS AND INHALANTS

Because of the great diversity of opinion regarding the use of antihistaminic agents in bronchial asthma, the following eighteen patients, all of whom presented typical allergic chest conditions, are reported upon in detail. The dosages given vary from 12.5 mg. to 200 mg. daily.

To take them in turn, one patient, aged ten, took 12.5 to 25 mg. when necessary for complete relief of mild symptoms, 50 mg. being necessary for severe wheezing, the effect lasting twelve hours. The patient required epinephrine (1:1000) subcutaneously in addition for extreme bronchospasm.

The second patient began with 50 mg. twice daily and now achieves complete relief with one 50 mg. tablet on arising. There were no side reactions. A third patient, aged eight, took 50 mg. twice daily with complete control of symptoms and no side reactions, and a fourth compared Perazil with epinephrine (by inhalation) and ephedrine-aminophylline (by mouth) and found that the Perazil gave the most complete relief, the effect lasting

four hours, although the patient could get equal relief with Amodrine tablets or Luasmin capsules, six of either being the daily requirement. Supplementary medication consisted of potassium iodide taken throughout the course of the study for all the medications listed.

One of the patients, aged sixty-two, emotionally unstable and sensitive to dust, tobacco smoke, and cooking fumes, found the taste of Perazil repellent, although she claimed that the tablets gave her greater relief than epinephrine by aerosol, aminophylline or ephedrine (gr. 3/8). She suffered, however, from side reactions on 50 mg. taken when necessary, which she stated reduced her attacks from an average duration of three hours to one hour, with freedom until the next attack occurred. She complained of light-headedness, nervousness, shakiness, and palpitations. Similar symptoms occurred with the use of ephedrine, aminophylline and epinephrine.

A number of patients achieved complete relief on 50 mg. taken at bedtime or on arising and retiring, although one of these, aged thirty-five and sensitive to dust and grass pollens, with exacerbation with exposure to range oil fumes, had only "slight improvement" with 50 mg. twice daily.

Some of the patients were unable to give fair pictures of the results, as for instance one, who on 50 mg. twice daily had no relief whatsoever, perhaps because of her clinically proven allergic condition which was associated with a moderate emphysema and bronchitis. An emotional factor may have intervened, in that the patient's husband was hospitalized during the time she was studied. She claimed, however, relief with Trimeton, Luasmin and Hydryllin, with no relief from Perazil, which she stated caused drowsiness, nausea, dizziness, and difficulty in walking.

One of the patients who presented a typical "cold" claimed relief for both it and her wheezing with 50 mg. twice daily, which almost completely controlled her symptoms, except for an occasional slight dyspnea, and another with a plantain, mould, ragweed and house dust sensitivity showed complete relief and no side reactions during the peak of the season. Another patient studied at the same time, who, in addition to her known sensitivities to Pyrethrum and house dust, presented a severe emphysema achieved "considerable relief" with two tablets daily and better relief on 150 mg. daily, but for very severe attacks took a Luasmin capsule at the same time.

The difficulties dependent upon accurate clinical evaluation are shown by a patient, aged sixty-three, who presented known dust, ragweed and food sensitivities, with moderate emphysema, who had exacerbations due to fatigue, barometric changes and exposure to fumes. The patient, a physician, had fair results with Benadryl and Hydryllin and claimed excellent results with Trimeton and Luasmin but no relief whatsoever with Perazil, although in doses of 200 mg. daily there were no side effects. Another typical patient, aged fifty-two, with perennial wheezing associated with seasonal exacerbations due to clinically proven grass and ragweed sensitivities and house dust, but suffering as well from a purulent sinusitis and moderate emphy-

sema as well as bronchitis, had no relief from 50 mg. four times daily. There were, however, no side reactions at this dosage level.

HAY FEVER AND BRONCHIAL ASTHMA

In all, there were thirty patients who suffered both from hay fever and bronchial asthma. Their reactions fell into no apparent pattern and the results were incapable of tabulation. They are, therefore, given brief individual description. Only three demonstrated side effects; one who took 50 mg, daily in two 25 mg. doses, with an occasional additional 25 mg. for symptoms following exposure, the ill effects being drowsiness and oral dryness. This patient had similar side reactions with Benadryl, Hydryllin and Trimeton. He was, however, free of symptoms on Perazil. The second patient complained of light-headedness and headache on doses of 50 mg. when necessary, which gave him partial relief of symptoms for two to three hours equal to the relief given by Trimeton, which caused the same type of untoward effect. The third patient, who took 50 mg. when necessary, complained of extreme drowsiness and palpitations with tachycardia, sufficient to warrant cessation of treatment.

Of the other patients, one who had suffered from hay fever and bronchial asthma of fourteen years' duration, seasonal and perennial in nature with sensitivities to grass, trees and ragweed pollen and house dust, was markedly improved being free of nasal and chest symptoms on 25 mg. taken when necessary. She preferred Perazil to Trimeton, Pyribenzamine and Luasmin capsules. A patient similar in clinical pattern, a boy aged ten, with grass and ragweed pollen, mould and house dust sensitivities, had excellent relief of his hay fever and wheezing on 25 mg. when necessary, and a third patient, aged four, took 12.5 mg. twice daily for complete relief of his hay fever and wheezing for three to six hours. A fourth patient, also aged four, was completely relieved of hay fever and wheezing for twelve to twenty-four hours on 25 to 50 mg. daily.

A patient, aged eight, sensitive to cat and horse dander, grass pollens and house dust was relieved on 25 mg. twice daily, with complete relief of both nasal and chest conditions, and another patient, who took 50 mg. daily and 50 mg. when necessary, was listed among those above as having drowsiness and dryness of the mouth, although the reactions were milder with Perazil than with the other antihistaminics. One patient on 25 mg. twice daily, and another on 50 mg. when necessary, had relief lasting up to twelve hours for both conditions.

The varying patterns are demonstrated by a patient on 25 mg. twice daily, who was able to do his farming on this dose, although sensitive to dust, cattle dander, feathers, mohair and horse dander. He stated that his nasal condition was better than it had been for the last ten years despite specific and symptomatic treatment. Of the other patients on the 50 mg. dosage level, moderate severe attacks were completely relieved, but very severe wheezing required Luasmin capsules or aminophylline suppositories.

One of these was sensitive to all of the animal danders, with which he was tested, to house dust, tree, grass, plantain and ragweed pollens and to moulds.

Of the patients who took larger doses, 75 to 100 mg. daily, one was able to eat foods which otherwise caused clinical symptoms, although for severe attacks she required ephedrine in small doses.

Not all the patients behaved equally. One who took 100 mg. daily had complete relief of her hay fever but only moderate relief of her wheezing, although another on the same dosage and with tree, grass, ragweed pollen sensitivities, with additional skin tests to Alternaria and house dust, found 100 mg. daily to give complete relief with no side reactions. Another patient in this same group, however, was not as completely relieved of the asthma, although her hay fever reacted well. She could not take Trimeton because it caused drowsiness and blurring of vision.

Of five patients on the 100 mg. dosage daily, one stated that Pyribenzamine gave quicker and more complete relief and refused to continue with Perazil, although there were no side reactions. The others reported complete freedom of symptoms. One patient with hay fever and bronchial asthma, sensitive to horse dander, house dust and grass and ragweed pollens, achieved no relief whatsoever on 200 mg. daily of Perazil but was completely relieved by 50 mg. of Trimeton, there being no side reactions with either. The last patient of the series, suffering from hay fever, bronchial asthma and urticaria had complete relief of her nose and skin symptoms for twelve hours following a 50 mg. dosage, the asthma being only partially relieved and requiring epinephrine aerosol therapy every two to three hours. The same patient had previously had little or slight benefit from Pyribenzamine and Benadryl in 50 mg. doses, both causing drowsiness. There were no side reactions with Perazil.

MIXED SYNDROMES

One patient, who had hay fever and poison ivy, reported that Perazil and Trimeton both relieved the pruritus as well as the nasal condition. A patient suffering from nasal pollinosis and atopic eczema responded better for her nasal symptoms than for the skin. A third suffered from hay fever and a chronic cough, with relief of the nasal symptoms, the throat condition being unaffected.

There were three patients who presented the complete syndrome of atopic eczema, hay fever and bronchial asthma. A young boy of twelve, who presented a picture of hay fever, bronchial asthma and atopic eczema, found that Perazil relieved his nasal symptoms completely on 25 mg. twice daily. His eczema was only slightly improved and his asthma unaffected. Another patient, aged eight, presenting the same syndrome, was free of nasal symptoms. He was so little relieved of his pruritus that Pyribenzamine ointment was prescribed with excellent results. A third patient found

that Perazil controlled the nasal symptoms, although he needed Trimeton ointment for his skin.

A fifty-nine-year-old patient suffering from a nasal coryza and severe nocturnal cough found his nose completely clear and his cough somewhat improved, as measured by longer periods of sleep during the night. Mercodinone (Merrell) completely controlled the cough.

SUMMARY

In all, 186 patients were treated with Perazil in doses of 12.5 to 200 mg. daily. The conditions studied were as follows: hay fever, seventy-five patients; vasomotor coryza, seven; urticaria, fifteen; intrinsic bronchial asthma, seven; atopic eczema, eight; vernal conjunctivitis, two; dermatitis herpetiformis, one; psoriasis, two; generalized pruritus, one; contact dermatitis, fourteen; atopic bronchial asthma, eighteen; hay fever and bronchial asthma, thirty; hay fever and poison ivy, one; atopic eczema and hay fever, one; atopic eczema, hay fever and bronchial asthma, three; and hay fever and allergic tracheitis, one.

Reactions were mild in one patient (not classified) and moderate, as evidenced by dry mouth, drowsiness and light-headedness, in five of the seventy-five patients with hay fever, one of thirteen with urticaria, three of thirty with hay fever and bronchial asthma, and one of eighteen with bronchial asthma. Reactions were usually associated with the doses in excess of 100 mg. daily. Although the results do not lend themselves to exact tabulations, they would appear to demonstrate Perazil the most effective of all the antihistaminic agents so far studied by the physicians who used it.

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MULTIPLE SCLEROSIS AND ALLERGY MANAGEMENT WITH HISTAMINE THERAPY

Part II

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ALLERGY as a term was suggested by Von Pirquet[47] in 1906. Since then, it has slowly become evident that the brain and meninges, the spinal roots and the peripheral nerves may be the sites of more or less severe allergic reactions.[38] Kennedy,[27,28] in 1936, directed attention to allergy as a possible basis in the production of multiple sclerosis. He stated: "Its episodes, its intermissions, the curability of its most acute crisis, its attack on the optic nerves, its neglect of sensory paths—all these things greatly resemble the happenings of localized allergic edemas after the central nervous system has come under fire. Further, the recent plaques in the rare autopsies of acute cases are not sclerotic; they are infiltrations by fluid of the nerve tissue surrounding blood vessels."

The same year Putnam[34] pointed to the essential similarity between encephalomyelitis and multiple sclerosis. In 1941 Putnam[36] expressed the view that the origin of encephalomyelitis is in some sense an allergic reaction, adding that "it seems not unreasonable to suppose that an instability of the clotting mechanism of the blood might be one aspect of allergy."

Shortly before this, Baer and Sulzberger[7] studied the role of allergy in a small group of patients with multiple sclerosis. Their conclusion in part was: "Of our thirty patients with multiple sclerosis who were completely studied, ten, or 33 per cent, presented evidence of personal or familial atopic disease or positive wheal reactions to skin tests or both."

There are many reports in the literature, and we have all seen patients with neurological symptoms produced by allergy. Urbach and Gottlieb[46] stated: "Paralysis of cerebral origin simulating vascular lesions may be due to angioneurotic edema of the brain caused by injection of foreign serums, as well as by internal absorption of allergens." Brickner[12] observed that: "Often a patient with multiple sclerosis, if pressed, may be able to recall a fleeting symptom years before, such as numbness of the fingers which disturbed his writing for perhaps an afternoon. On a basis of these mild, vague and transitory symptoms one is not justified in making a diagnosis of multiple sclerosis, but a prognosis of this disease should be considered." On this subject Lichtenstein[32] says: "The prognosis in multiple sclerosis is not as grave as many would have the profession believe. Some individuals have two or more mild attacks and never go on to develop the advanced form of the disease."

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In 1940 Ferraro and Jervis,[14] also in 1948 Kabat,[25,26] Mayer,[25] Wolf and Bezer[26] reported the production of acute disseminated encephalomyelitis in rhesus monkeys, by the injection of rabbit or monkey brain or monkey spinal cord as an emulsion.

ALLERGY

Following the report of Horton and his co-workers Wagener, Waltman and Aita[23] in 1944, on the treatment of 102 cases of multiple sclerosis with the intravenous administration of histamine diphosphate, we began the study of the disease on an allergy basis. This approach was made in the same manner as in the study of angioneurotic edema, migraine, bronchial asthma, urticaria or any other allergic condition. Complete histories were carefully taken, all were tested for their sensitivity to foods, epidermals, molds, fungi, pollens and miscellaneous allergens. Elimination diets were used, and careful observations were made as to food offenders.

A thorough survey was made as to the precipitating or aggravating factors with reference to pregnancy and trauma. All patients were studied in relation to their emotional stability.

In all, 152 cases were studied and treated, eighty-seven females and sixty-five males. Their ages varied from fifteen to forty-nine years at onset, with an average age of 29.8 years. All except three had lived most of their lives in the northern half of the United States and Canada. There were nineteen acute cases and 133 of the chronic progressive type.

Many of the patients suffered from several different types of allergy. In some patients emotional upsets, pregnancy, and trauma appeared to be the "trigger" that precipitated the disease.

D-TUBOCURARINE

As previously reported,[24] we used d-Tubocurarine in oil and wax,* with muscle re-education, very successfully as an aid in our treatment. This medication relieved tremors, spasticity, incontinence and rigidity in nearly all patients. It was given deep into the muscle in doses that varied from 7.5 mg. every fourth day up to as much as 120 mg. daily. There was a wide range in dosage among patients, the effects in some lasting as long as ninety-six hours, in others only twelve to sixteen hours.

The action of the d-Tubocurarine in oil and wax was startlingly good. This preparation gave prolonged action with constant effects. It gave an immediate feeling of relaxation and comfort to the tense, spastic patients. The first dose often gave them the first comfortable night's sleep they had had in years. Incontinence and frequency of urination were improved or controlled in a very short time in every case. Constipation, the "bugaboo" of multiple sclerosis, was relieved in most patients within a few weeks. Tremors were markedly reduced in all cases. Voluntary movements

*Supplied through the courtesy of the Abbott Research Laboratories.

previously blocked by spastic rigidity were made possible, and patients were able to move hands, arms, legs and other parts of their body in varying degrees approaching normal. These limbs had previously been paralyzed or uncontrollable through spasticity and tremors.

Some patients were able to go for a month to six weeks without a noticeable return of tremors, muscle rigidity or spasticity. Because of this, patients were able to take vacations from treatment at varying intervals with a good effect on their morale.

We have given over 30,000 doses of d-Tubocurarine in the last eighteen months without a single undesirable reaction. Neither has there been any tendency to habituation in any case. As a matter of fact, the patients all seem to want to decrease their dose as rapidly as possible. This is because the accumulative effect is prone to produce uncomfortable dizziness, slight visual symptoms or other side effects, unless the amount of the drug given is gradually decreased. Also, at certain times after the drug has been administered over a period, there will develop a "stiffness" or lack of power in all four limbs and lower jaw. This condition is relieved by withdrawal of the drug for a week or ten days.

MANAGEMENT

Complete allergy management was the basis of our therapy. Under this therapy allergenic extracts were used as indicated. For the typical "head colds" of multiple sclerosis noted by many writers,[17,41,39] we use respiratory vaccines.

Nearly all of our 152 cases showed some form of allergic sensitivity. Those with multiple food allergies apparently were more spastic than those with other allergies. It is generally conceded that foods are the worst offenders in cerebral allergies.[10,42,49,50,51] We did not depend on scratch tests wholly, but also used diet diaries and elimination diets. Carefully observing the effects of various foods from a clinical standpoint, several patients were placed on Rowe's[40] cereal-free diet with apparently very good results. Focal infections were looked for, and cleared up when possible. Eye symptoms and visual fields[8,11,16,19,21,48] were carefully checked. Improvement in these was used as an index for our therapy, retrobulbar neuritis being considered an early episode of multiple sclerosis.

If exacerbations can be definitely prevented, the normal tendency of the disease is one of recovery.[37] Realizing this, we instructed all patients to avoid chilling,[44] accidents,[18] over-exertion[45] and emotional upsets.[31] Female patients were told of the dangers of pregnancy[29,33] in multiple sclerosis.

The criterion of the success of any treatment of multiple sclerosis should be the prevention of relapses.[35] An attitude of rejection in therapy is easy to develop in regard to this disease.[13] As our study is based on the assumption that allergy is the cause of multiple sclerosis, histamine becomes the medication of choice. Horton[22] and his co-workers seem in-

clined to relate any recovery and improvement to vasodilatation in the central nervous system resulting from repeated injections of histamine. On the other hand, Ferraro[15] speculated on the beneficial effects of histamine's being the result of the production of histamine-specific antibodies. Kwiatkowski[30] has shown that all living tissue contains histamine except the central nervous system, motor nerves and sensory nerves from special sense organs. This was brought to our attention during a conversation with Dr. Horton. We are of the opinion that the dramatic improvement in acute cases and the improved condition of the chronic cases under histamine therapy is in some way related to this absence of histamine in tissues of the central nervous system. The reason for the effectiveness of this therapy will not be known until research gives us greater knowledge of the biochemical and immunological factors involved.

HISTAMINE

We administer histamine by four different methods: subcutaneous, intravenous, continuous infusion and by iontophoresis. Our patients are given histamine diphosphate intravenously to the point of tolerance. They receive 2.75 mg. of histamine diphosphate in 250 c.c. normal saline daily, and others at times a continuous infusion[43] of 11 mg. histamine diphosphate in 1,000 c.c. of normal saline at a rate of 30 drops per minute every six hours, alternating with 11 mg. histamine diphosphate in 1,000 c.c. of 5 per cent glucose solution. This continuous infusion is given for periods of twenty-four, and in some cases forty-eight hours. Our best results were in the cases that were able to take the larger amounts. In the cases where histamine had been a failure before coming to us, we believe that too little had been given for too short a time. A number of these patients when given larger amounts responded very satisfactorily. Using histamine, we accomplished two purposes: first, the hyposensitization of the patient to the histamine reactions of allergy; and second, the benefit derived from histamine as a vasodilator, being the most effective vasodilator known on the tissues of the central nervous system.

In our series we have administered histamine diphosphate intravenously over 25,000 times and have had no noticeable reactions.

We found, as did Benson and Horton,[9] that the pulse and blood pressure are only temporarily affected to a slight degree by repeated intravenous injections of histamine.

The patients were also given .275 mg. per c.c. of histamine diphosphate subcutaneously. The dose beginning at .1 c.c. daily was increased in the usual manner. From a therapeutic standpoint, the same size dose of histamine by the subcutaneous route is ten times more effective than it is by the intravenous.[20] Following the release from active treatment, we advise our patients to take histamine subcutaneously once a week for the rest of their lives. This, as a prophylaxis against exacerbations of multiple sclerosis. The usual dose is .5 c.c. of a .275 mg. histamine diphosphate per c.c. of solution.

Recently Abramson[1,2,3,4,5,6] developed the technique of administering histamine by iontophoresis. This method is very simple, only involving the passage of histamine into the skin, driven by a galvanic current which forms deposits in the pores of the skin. Under the electrode area a large wheal is formed containing histamine, which is slowly absorbed. We believe that this way of administration combines effects of the subcutaneous, intravenous and continuous infusion methods.

The technique employed is as follows: Three folds of canton flannel with 10 c.c. of a 1 per cent solution of histamine diphosphate† are applied to the anterior aspect of the forearm. Contact is then made with the positive electrode which is held in place by an elastic bandage. Canton flannel damp with water, is applied to the other forearm and the negative electrode applied in the same manner. The dosage is controlled by the amount of current used and the length of time of the treatment. We use 2 to 8 milliamperes for fifteen to thirty minutes, according to the reaction of the patient. To overcome hyperacidity, 15 grains of bicarbonate of soda is given by mouth before each treatment.

The principal advantages of histamine iontophoresis are: it is well adapted for home use, the apparatus is inexpensive, and sterile equipment need not be employed. The typical histamine flush occurs within five to ten minutes, and is as intense as that produced by the intravenous method. Absorption from the skin deposits is slow, as the flushed area around the wheal remains from six to seventy-two hours after the treatment.

We do not use iontophoresis until our patients have had at least thirty intravenous injections of histamine. Some had over 200 before starting. Also, only those who have shown marked improvement under intravenous histamine therapy are given the drug by the electrophoresis method. If they continue to show improvement over a period of six to eight weeks, we release them for home treatment.

At this time we are treating sixty-two patients with multiple sclerosis by histamine iontophoresis, twenty-five at home and thirty-seven in the hospital as out-patients. The results have been very satisfactory in all except two cases. These two patients said they felt better under intravenous therapy, so they were returned to that type of treatment. Both of these are wheel-chair cases of long standing. One is very spastic, and the other has a very painful complicating osteoarthritis. All of the other sixty patients appear to improve as well or better under iontophoresis as they had under intravenous histamine.

With histamine therapy in most cases there is a temporary increase in muscular co-ordination and strength. This period of improvement lasts longer with iontophoresis than it does when the histamine is given by the intravenous method.

†Supplied through the courtesy of the Abbott Research Laboratories.

TABLE I. SIXTY-TWO MULTIPLE SCLEROSIS CASES RECEIVING HISTAMINE IONTOPHORESIS

St. Joseph's Hospital, Tacoma, Washington

Case No. Age Occupation	Allergies	Type	Symptoms On Admission	d-Tubocurarine in oil and wax	Number of Intravenous Histamine Diphosphate Injections	Number of Histamine Iontophoresis Treatments	Present Condition
1. Mrs. L.A. 50 H.W.	Urticaria Foods	Ch. Prog. 1933	Spastic Paraplegia Paresthesia Dyspharthria Pollakiuria Amblyopia Wheel Chair	7.5 mg. 3 times weekly	131	24 Home treatment after tenth	Walking, symptoms all markedly improved.
2. Miss M.B. 31 Graduate Nurse	Rhinitis	Ch. Prog. 1944	Paresis Euphoria Hippus Strabismus	7.5 mg. 3 times weekly	74	33 Home treatment after tenth	Generally improved.
3. Miss I.B. 35 Office	Neuroedema	Acute	Dysarthria Amblyopia Paresis Pollakiuria	15 mg. 2 times weekly	78	22 Home treatment after tenth	Symptom free.
4. Mrs. M.B. 33 H.W.	Pollens Epidermals	Ch. Prog. 1944	Dysarthria Paraplegia Pollakiuria	15 mg. 3 times weekly	69	36 Home treatment after tenth	Improved.
5. Mr. L.B. 49 Barber	Human Hair Foods	Ch. Prog. 1938	Spastic Paraplegia Cane case 3 years	7.5 mg. 3 times weekly	146	23 Home treatment after fifteenth	Walks without cane.
6. Mrs. M.B. 29 H.W.	Eczema Molds Pollens Foods	Ch. Prog. 1938	Dysarthria Quadriplegia Oscillopsia Pollakiuria Bed-fast	30 mg. 3 times weekly	142	23	Walking in walker wheel chair.
7. Mrs. L.C. 42 H.W.	None	Acute	Paresis Paresthesia Dysarthria Pollakiuria	15 mg. 3 times weekly	30	26 Home treatment after tenth	Symptom free.
8. Mrs. L.C. 43 H.W.	Foods Epidermals	Ch Prog. 1930	Paraplegia Pollakiuria Amblyopia Wheel chair	15 mg. 3 times weekly	129	22 Home treatment after tenth	Generally improved. Paraplegia same.
9. Mr. F.C. 53 Fruit shipper	Foods	Ch. Prog. 1943	Parasis Dysarthria Oscillopsia Amblyopia	15 mg. 3 times weekly	65	39 Home treatment after tenth	No objective improvement.
10. Mrs. M.C. 44 H.W.	Rhinitis Pollens	Acute	Paresis Paresthesia Dysarthria Pollakiuria	15 mg. 3 times weekly	30	12 Home treatment after tenth	Symptom free.
11. Mrs. H.C. 56 H.W.	Foods	Ch. Prog. 1930	Amblyopia Hippus Paresis Strabismus	15 mg. 3 times weekly	72	11 Home treatment after sixth	Objectively symptom free.
12. Mr. R.D. 44 Sheet Metal Worker	Asthma	Ch. Prog. 1944	Spastic Paresis Pollakiuria Paresthesia	30 mg. 3 times weekly	139	15	All symptoms improved.
13. Mrs. R.D. 37 H.W.	Molds	Ch. Prog. 1942	Paraplegia Strabismus Hippus Paresthesia	30 mg. 3 times weekly	112	41 Home treatment after twentieth	Slight general improvement.
14. Mrs. L.E. 36 Graduate nurse	Foods Pollens	Ch. Prog. 1944	Paraplegia Amaurosis Dysarthria Pollakiuria	22.5 mg. twice daily	187	36 Home treatment after ninth	No objective improvement.

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Case No. Age Occupation	Allergies	Type	Symptoms On Admission	d-Tubocurarine in oil and wax	Number of Intravenous Histamine Diphosphate Injections	Number of Histamine Iontophoresis Treatments	Present Condition
15. Mr. R.E. 42 Druggist	None	Ch. Prog. 1941	Urinary incontinence. Hippus Spastic Paresis	30 mg. 3 times weekly	158	27 Home treatment after tenth	Symptom free.
16. Mr. C.F. 41 Paper-maker	Newspaper	Ch. Prog. 1944	Amblyopia Dysarthria Spastic Paresis all limbs Cane case	30 mg. 3 times weekly	134	39	Generally improved. Walks without cane.
17. Mr. C.F. 46 Grocer	Foods	Ch. Prog. 1941	Spastic Paresis all limbs Dysarthria Amblyopia	30 mg. 3 times weekly	64	24 Home treatment after tenth	Slight improvement.
18. Miss P.F. 42 Seamstress	Epidermals Molds	Ch. Prog. 1944	Hippus Spastic gait Pollakiuria Paresthesia	15 mg. 3 times weekly	96	47	Marked improvement. Gait nearly normal.
19. Mr. F.G. 40 Steam Engineer	Foods	Ch. Prog. 1942	Urinary incontinence. Spastic gait. Paresthesia.	15 mg. 3 times weekly	203 Continuous infusion 48 hours, 8 sessions.	34	Objectively symptom free. Gait normal.
20. Mr. J.G. 56 Farmer	None	Ch. Prog. 1930	Quadriplegia Urinary incontinence. Strabismus Wheel Chair.	30 mg. daily	148	3 Returned to Intravenous.	Slight objective improvement.
21. Mrs. A.H. 36 H.W.	None	Ch. Prog. 1946	Spastic gait Paresthesia	15 mg. 3 times weekly	56	2	Improvement in gait.
22. Mrs. D.H. 36 Office	Foods Pollens	Ch. Prog. 1931	Amblyopia Dysarthria Diplopia Paresthesia Spastic gait	15 mg. 3 times weekly	96	45	Objectively symptom free. Gait normal.
23. Mr. J.H. 29 Estimator	Epidermals Foods	Acute	Paresthesia Dysarthria Diplopia Spastic gait	22.5 mg. 3 times weekly	49	33	Objectively symptom free.
24. Mrs. E.H. 29 H.W.	Rhinitis	Ch. Prog. 1941	Paraplegia Euphoria Amblyopia Wheel chair.	22.5 mg. 3 times weekly	186	13	Slight objective improvement.
25. Mr. G.H. 67 R.R. worker	None	Ch. Prog. 1918	Dysarthria Spastic Paresis Strabismus	15 mg. 3 times weekly	30	20	All symptoms improved.
26. Miss M.J. 49 Office	Foods	Ch. Prog. 1940	Spastic Quadriplegia Urinary incontinence. Amblyopia. Bed fast.	30 mg. twice daily	173	21	Incontinence relieved. Wheel chair. Marked improvement.
27. Mrs. A.J. 32 H.W.	None	Acute	Diplopia Dysarthria Spastic gait.	15 mg. 3 times weekly	36	52 Home treatment after tenth	Symptom free.

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28. Mr. C.K. 40 Druggist	Epidermals Molds	Ch. Prog. 1943	Amaurosis Dysarthria Hippus Spastic Quadriplegia Urinary incontinence. Whee chair.	30 mg. 3 times weekly	221 Continuous infusion 24 hours twice. 48 hours once.	39 Home treatment after tenth	Incontinence improved markedly. Some improvement objectively in all other symptoms.
29. Mrs. A.K. 24 H.W.	Rhinitis Pollens	Ch. Prog. 1946	Spastic Quadriplegia Dysarthria Diplopia Wheel chair	15 mg. twice daily	127	26 Home treatment after eleventh	Imrpovement all symptoms. Walks in walker
30. Mrs. V.K. 26 H.W.	Foods Epidermals	Ch. Prog. 1939	Paresthesia Spastic Paresis all limbs	15 mg. 3 times weekly	167	29	Objectively symptom free
31. Mrs. C.K. 32 H.W.	Foods Rhinitis	Ch. Prog. 1941	Amblyopia Dysarthria Spastic Quadriplegia	22.5 mg. daily	138	40 Home treatment after tenth	Slight improvement
32. Mrs. B.L. 38 Teacher	None	Ch. Prog. 1944	Paresis Diplopia Paresthesia	15 mg. 3 times weekly	76	2	Slight improvement
33. Mrs. E.L. 48 H.W.	Foods	Ch. Prog. 1933	Spastic Quadriplegia Diplopia Wheel chair	30 mg. twice daily	147	35 Home treatment after tenth	No objective improvement
34. Mrs. S.L. 42 H.W.	None	Ch. Prog. 1941	Pollakiuria Spastic Paresis Amaurosis	15 mg. 3 times weekly	102	6	Marked improvement pollakiuria
35. Mr. W.M. 37 Office	Heat	Ch. Prog. 1940	Paresis Strabismus Spastic gait	15 mg. daily	96	16	No objective improvement
36. Mrs. A.M. 18 H.W.	None	Acute	Paraplegia Urinary incontinence. Strabismus Amaurosis Bed-fast	30 mg. twice daily	132	32	Marked improvement all symptoms. Walking unassisted.
37. Mr. F.M. 43 Woodsman	None	Acute	Retrobulbar neuritis. Vision:— right 20/400 left 20/160	none	32	3	Vision:— right 20/30 left 20/40
38. Mr. E.M. 36 Salesman	Pollens Rhinitis	Ch. Prog. 1942	Spastic gait Dysarthria	15 mg. 3 times weekly	81	4	Slight objective improvement
39. Mr. E.N. 54 Office	Foods	Ch. Prog. 1941	Hemiplegia Dysarthria	15 mg. 3 times weekly	30	11	Marked improvement
40. Mr. O.R. 34 Automobile mechanic	None	Ch. Prog. 1931	Spastic paraplegia. Pollakiuria Paresthesia Amblyopia Wheel chair	30 mg. 3 times weekly	167	37	All symptoms improved
41. Mr. R.O. 48 Lumberman	Pollens	Ch. Prog. 1939	Spastic gait. Diplopia Hippus Paresthesia	15 mg. 3 times weekly	30	15 Home treatment after tenth	Gait nearly normal

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42. Mrs. H.O. 36 H.W.	Molds Epidermals	Ch. Prog. 1939	Spastic Quadriplegia Wheel chair	15 mg. 3 times weekly	66	46 Home treatment after tenth	Slight objective improvement
43. Mrs. C.E. 40 H.W.	None	Acute	Paraplegia Diplopia	15 mg. 3 times weekly	143	35	Symptom free
44. Mr. I.P. 55 Laborer	Rhinitis	Ch. Prog. 1931	Spastic gait Paresis Pollakiuria Amblyopia	15 mg. 3 times weekly	224	29	Gait improved
45. Mr. A.R. 47 Machinist	Molds	Ch. Prog. 1940	Spastic gait Paresis Poiiakiuria Amblyopia	15 mg. 3 times weekly	78	46 Home treatment after tenth	Improvement all symptoms
46. Miss M.R. 23 Office	Foods	Ch Prog. 1944	Spastic Paraplegia Pollakiuria Oscillopsia	15 mg. 3 times weekly	81	44	Slight objective improvement
47. Mr. J.S. 40 Woodsman	None	Ch. Prog. 1943	Amblyopia Pollakiuria Dysarthria Spastic Paraplegia	15 mg. twice daily	304	11 Returned to intravenous	Improvement in all symptoms
48. Mr. N.S. 53 Hydro-electric worker	Foods Molds	Ch. Prog. 1928	Spastic Hemiplegia Pollakiuria	15 mg. 3 times weekly	163	32	Slight improvement
49. Miss B.S. 44 Bookkeeper	None	Ch. Prog. 1943	Diplopia Spastic gait	15 mg. 3 times weekly	129	39	Objectively symptom free
50. Miss A.S. 46 Teacher	Hay fever	Ch. Prog. 1939	Diplopia Dysarthria Paresis Pollakiuria Spastic gait	7.5 mg. 3 times weekly	137	52	All except gait, improved
51. Mr. W.S. 40 Office	Rhinitis	Acute	Paresthesia Paresis Amblyopia Spastic gait	15 mg. 3 times weekly	52	26 Home treatment after twenty-second	Objectively symptom free
52. Miss G.S. 44 Telephone Operator	Eczema Epidermals	Ch. Prog. 1941	Spastic Paresis all limbs Pollakiuria Amblyopia Cane case	15 mg. 3 times weekly	182	13	Marked improvement all symptoms. Does not use cane.
53. Mrs. G.S. 55 H.W.	Foods	Ch. Prog. 1924	Spastic gait Paresthesia	7.5 mg. daily	151	52	Some objective improvement
54. Mr. F.S. 53 Engineer	None	Ch. Prog. 1936	Strabismus Amaurosis Spastic Quadriplegia Bed-fast	30 mg. twice daily	178	24	Slight improvement Wheel chair

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55. Mrs. L.W. 38 H.W.	Foods	Ch. Prog. 1941	Hemiplegia Dysphasia Amaurosis. Complete incontinence; Bed-fast.	30 mg. twice daily	78	30	Walks unassisted
56. Mrs. M.W. 28 H.W.	Molds	Ch. Prog. 1946	Spastic Paresis Dysarthria Pollakiuria	15 mg. 3 times weekly	168	39	All symptoms improved
57. Mr. J.W. 39 Office	Asthma Eczema Hay fever	Ch. Prog. 1941	Spastic Paraplegia Paresthesia Pollakiuria Wheel chair	30 mg. 3 times weekly	207 Continuous infusion 48 hours. Six sessions	45	Stands alone. Walks on crutches. All symptoms markedly improved
58. Mrs. M.W. 34 H.W.	Foods	Ch. Prog. 1943	Amaurosis Dysarthria Very spastic Quadriplegia Bed-fast	30 mg. twice daily	153	26	Walks with assistance
59. Mrs. G.W. 56 H.W.	Rhinitis	Ch. Prog. 1930	Paraplegia Paresthesia Pollakiuria Wheel chair	15 mg. 3 times weekly	104	52 Home treatment after thirtieth	Walks by holding to furniture
60. Mr. S.W. 39 Lumberman	None	Ch. Prog. 1939	Quadriplegia Urinary incontinence. Amaurosis Dysarthria, Bed-fast	15 mg. twice daily	130	65	All symptoms improved. Wheel chair
61. Mr. M.W. 61 Yeast-maker	Molds	Ch. Prog. 1925	Urinary incontinence. Spastic Paraplegia Wheel chair	7.5 mg. 3 times weekly	156	58 Home treatment after tenth	All symptoms improved
62. Mr. F.Z. 49 Tel. Co.	Rhinitis Foods	Ch. Prog. 1940	Spastic Hemiplegia Pollakiuria	15 mg. 3 times weekly	104	44 Home treatment after thirtieth	Marked improvement

COMMENTS

The regimen of treatment as outlined has resulted in improvement in a large majority of the patients at our Multiple Sclerosis Clinic. This is spectacularly true in the acute cases. Of these, we have treated nineteen, only one showing no improvement. All of the others became objectively symptom free in a short time. There has not been a major exacerbation among these patients. The remissions at this time have lasted from three months to over two years.

The 133 with chronic types have not responded as dramatically as the acute ones. However, nearly all who have remained under treatment for

three months or more have shown improvement in varying degrees. As is to be expected, some of these chronic patients become discouraged and stop treatment in a few days or weeks if no marked improvement is noted. However, the more or less mass treatment in our clinic tends to increase the morale of the patients in general. While one may not be improving as rapidly as hoped for, they see others progressing and this keeps their spirits up. Thereby, those who improve act as an inspiration on the others. d-Tubocurarine in oil and wax has been of great value in helping build morale, as it quickly helps in the control of spasticity, tremor and incontinence. By simple orthopedic procedures and muscle re-education, the effectiveness of d-Tubocurarine is increased in the chronic cases.

Tabulating the results of our treatment up to date, we find the following:

Objectively symptom-free, returned to normal activity	25
Marked improvement objectively, remained on full employment	13
Improved objectively, activities limited	37
Slight improvement objectively	29
Improved subjectively	28
No improvement subjectively or objectively	12
Worse than at the beginning of treatment	3
Died, since treatment started	5
TOTAL	152

The object of therapy in multiple sclerosis is the prevention of exacerbations. When a definite allergy can be shown, it is obvious that this should be eliminated. The difficulty is that in most cases there is more than one allergic offender. It is not possible in each case to determine every substance which can produce a reaction. For this reason even careful allergy management must have an over-all adjunct to prevent relapses in this disease. In our cases, histamine is that agent. There have been practically no major and very few minor exacerbations among our patients who received this therapy regularly. To this end, iontophoresis provides an easy, safe and effective method for the administration of histamine in the home of every sufferer from multiple sclerosis.

CONCLUSIONS

1. Under allergy management and histamine therapy the exacerbations of multiple sclerosis are reduced as to number, and the remissions are lengthened as to time.

2. Following the establishment of a definite diagnosis of multiple sclerosis, some form of histamine therapy is indicated for the balance of the patient's life.

3. The earlier treatment is started, the more successful it is. In the acute cases, the chances of early and long extended remissions are good.

4. In the chronic cases, varying degrees of improvement occur while

under treatment; the improvement appears to continue as long as the patient continues treatment.

5. Treatment as given at our clinic does not cure, but merely arrests symptoms, as is in the case of any other allergic condition. However, it does hold out hope to the patients for their future. By this regimen we have made ambulatory or wheel-chair cases out of bed-fast ones. Also, we have taken wheel-chair patients and made them ambulatory. Still others have become symptom free and remained so without an exacerbation up to periods of over two years. In doing these things for these patients we feel that much has been accomplished.

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DISCUSSION

CHAIRMAN ORVAL R. WITHERS: We will now have the discussion of Dr. Jonez' paper, and I am sure we will all be glad to hear what Dr. Horton, who has done a good deal of work along this line, will have to say about it.

DR. BAYARD T. HORTON: I am personally very glad that Dr. Jonez has brought up the subject of multiple sclerosis, even in the American College of Allergists. Perhaps some of you think it is out of place here, but I for one think that mul-

tiple sclerosis represents an allergic disease, and furthermore, I am inclined to think that it presents the biggest challenge in this College at the present time.

It is a challenge for the medical profession. Multiple sclerosis is one of the most common diseases affecting the central nervous system and it is far more common than poliomyelitis. As I have said before, we will require a March of Dollars—not the March of Dimes—in approaching this problem.

I feel reasonably sure—and many others agree with me—that we as physicians see only the patients who do not make spontaneous recoveries. This is certainly true of poliomyelitis. Many patients have it in a mild form and recover and never see a physician. The same thing is true with multiple sclerosis.

Two weeks ago I had lunch with one of the professors of neurology in the East, and he expressed that same thought. There are certain fundamental facts which all physicians must keep in mind when thinking and dealing with such a complex problem as multiple sclerosis. In the first place, it is a demyelinating disease, and there are many others, other than multiple sclerosis.

But the two facts I would like to emphasize that are important are as follows: In the nerve tissue, nerve elements in the central nervous system do not regenerate. For example, if a nerve cell is injured to the point that it dies, or if one of the fibers breaks, the nerve cell does not grow back nor does the broken fiber grow back together. What happens? The supporting structure in the central nervous system is the neurocele. It is comparable to connective tissue on the outside of the central nervous system, and so neurocele plays the predominant role in producing signs and symptoms of most central nervous system diseases, and the neurocele grows in to take the place of nerve elements that die or fibers that are broken.

But the scarred tissue in the central nervous system won't transmit nerve impulses, and therefore the patient with multiple sclerosis gets well but it is a question as to whether he gets well with or without scar formation. It is the same principle that is applied to the cornea. If an individual has an ulceration on the cornea, it may heal with scarring or without scarring. If it heals with scarring, you have an opaque tissue which you try to see through. You can't do it.

So in the central nervous system, it is not a question of healing when the patient dies. He does not die of multiple sclerosis. He dies of something else and when you do the post-mortem examination, you find scarring and you have healing, but that is the challenge to the medical profession. Prevent scarring in the central nervous system and your individual comes back to normal.

The second important fact, I wish to emphasize is that the central nervous system is enclosed in a bony cavity and there is little or no room for expansion. Hence, a little edema will produce a maximal amount of disturbance when it affects the central nervous system, whereas on the skin you call it hives or giant urticaria and do not think much about it. It is this second fact that produces so many dramatic signs and symptoms.

I saw two patients yesterday morning—one a young woman from New York City. Last week I saw her totally blind in the right eye, and the next day she had normal fields and normal vision. You think it can't happen, but it does. It happens many, many times.

The other patient was a young man who had been in the Navy and who had normal vision, but for some unknown reason he went blind. His visual fields were coming back to normal. So keep in mind the fact that there is no regeneration, and secondly, remember that an edema exists which will produce symptoms out of all proportions to what you might expect.

Finally, early dagnosis and early attempts at treatment are of paramount importance. If you wait until the individual has scarring in the central nervous system, you will never change that clinical picture. It is impossible to do so. Don't be

afraid—one has to lose his sense of fear in approaching the problem of multiple sclerosis.

It is a tremendous field and an allergic disease with which you are dealing, and it should be—and I hope it will be—a challenge to you when you go back home to face these problems. Dr. Jonez, I am very happy to say, has lost his sense of fear, and he is pushing ahead, and don't throw stones at him because it is not justifiable.

CHAIRMAN WITHERS: Is. Dr. Boshes here? Will you continue with the discussion?

DR. LOUIS D. BOSHES: It is indeed an honor for me to be on this rostrum, particularly after hearing and seeing Dr. Horton again, and it is a privilege to discuss this most interesting paper of Dr. Jonez' on multiple sclerosis. Thus far, this has been a hopeless disease, and we neurologists who treat these patients welcome any research on that which will throw light on management. As to the author's components, our observations, however, are not entirely in keeping with those of the author and I will take these up one by one.

We agree that patients with multiple sclerosis may have allergies, but the question is: do these allergies cause lesions in the central nervous system exactly as in the multiple sclerosis? To my knowledge, according to my reading and observations, they do not. In fact, in one of the author's references, I reviewed carefully the work of Rosenow with streptococcal bacterial injections. He admitted the cause of death in animals was obscure, in those that died after the streptococci were no longer isolated in the brain or blood and were no longer demonstrated in the pathological areas. Lesions he produced with inoculated streptococci did not look like the classical picture seen in typical multiple sclerosis.

As to the work mentioned by the author with d-Tubocurarine in oil suspension, we, like many others, have repeated the work of Schlessinger of Columbia, who was one of the first to use this mixture in the treatment of spasticity in multiple sclerosis. In his words, he reported improvement in function and relaxation of involved extremities, lasting up to three to five days following an injection of .5 to 2.5 c.c. of the solution, and he stated, "Spasm, spasticity and rigidity are affected in order of decreasing efficiency."

In the Department of Nervous and Mental Disease of Northwestern University various members took up work with d-Tubocurarine in the Paraplegic Service of the Veterans Hospital in Hines, Illinois, where several paraplegics were put on this preparation; and at the meeting last year of the Chicago Neurological Society, my brother stated there was no release of spasticity at all. Other patients with multiple sclerosis were evaluated, such as these, elsewhere. A typical group of research men, and I will name them—Nathanson and Lesser and Dresser—reported their own work as well as that of others in the *Archives of Neurology and Psychology* of June, 1948, and stated that no improvement was offered in active motion, passive motion or functional use in spastic diseases due to the involvement of the central nervous system.

In a group of twelve multiple sclerosis cases on the Neurological Service of Dr. Autff and myself at Cook County Hospital, we repeated the classical work of Schlessinger and arrived at conclusions that there were no beneficial effects. In fact, Donald Monroe of the Boston Harvard Medical School, using distilled water as controls, reported similar effects were reached.

There is no drug known, including even the latest one you have read about in the *Journal of the American Medical Association*—Parpanit, which is a synthetic atropine-like drug with few side actions—that can control the tremor of cerebellar origin such as we see in multiple sclerosis. It is physiologically impossible to control

spasticity of limbs by drugs and to control the bladder at the same time. That is a neurological paradox.

In general, the author's study is based on the assumption that allergy is the cause of multiple sclerosis. In proof, we hope this would be true because if that were so, all studies could be in that direction and we would be very happy to go along with that.

As far as the vasodilating drugs are concerned, we know of the oral and parenteral ones. No clear-cut long-time beneficial effects have been reported in the use of the oral medications. You all know the work of Dr. Horton, I am sure. Although histamine is the most valuable of the vasodilating drugs, there is no critical proof contrariwise that this drug is an aid in multiple sclerosis. Actually, as the reports come through, more and more there is proof to the contrary.

It is important to remember that the disease has spontaneous remissions, which Dr. Horton has mentioned. Retrobulbar neuritis, in a case which was presented to you a few moments ago, usually clears up with no treatment. Some cases usually subside spontaneously and may not ever appear again. Most cases go untreated anyway and are permitted to lie around. Any treatment is of aid for a while, especially if the patient gets physiotherapy at the same time. Many nonparalyzed, atrophic and weak muscles become functional again by being "used again."

In conclusion, the concensus of the country is that there is no treatment for multiple sclerosis as yet. We must seek for some stabilized treatment to prevent relapses—not in the expectation that myelin will be regenerated or scar dissolved. We hope the allergists will continue their search in that direction.

However, the rigid criterion for improvement used by neurologists must also be used by allergists. It has been a pleasure, indeed, to review the paper by the author and to hear Dr. Horton.

CHAIRMAN WITHERS: Differences of opinion cause us to have more discussion, so we will continue. Dr. Abramson, would you like to make a few remarks?

DR. HAROLD A. ARRAMSON: I think that this difference of opinion is of importance and should be discussed openly because of the rather pessimistic remarks of the preceding speaker. Dr. Boshes stated that there was a consensus of opinion through the country on rigid criteria concerning the therapy of multiple sclerosis as far as neurologic opinion is concerned. I'm afraid that I must disagree with the statement that there is unified opinion amongst neurologists. Even if what Dr. Boshes said is true, that there is a consensus of opinion, I doubt that he can speak for all of the neurologists in the country or for the "rigid criteria" in a disease as complicated as multiple sclerosis. Or should I say in *the diseases of multiple sclerosis?* Let me tell you why.

When I heard Dr. Horton speak at the Pennsylvania Hotel in New York last year, on his technique of administering histamine intravenously in multiple sclerosis, I was very much impressed by the fact that in this hopeless disease, Dr. Horton had developed a method that had a fair theoretical background, was reasonably good psychotherapy, and also had pharmacologic rationale behind it. It appeared to me that it was worthwhile trying. However, against the administration of histamine was the difficulty of giving it intravenously for sixty to ninety days or more. As you know, I have had a fair amount of experience in electrophoresis, and about a year ago I developed a method of giving histamine by electrophoresis so that the rate of administration would be equivalent to the intravenous drip. As Dr. Jonez has pointed out, he has used this method and found the pharmacologic and physiologic effects which I noted. When the blood pressure dropped to 90/50, I expected the patient to collapse. In the majority of the cases, rather than collapse, there was increased muscular co-ordination. That is, instead of having the patient

with a low blood pressure become weaker, he got up and walked a good deal better. It might be that this is only psychotherapy. However, the severe flush and the change in blood pressure make me feel that to call the reaction psychotherapy, with the profound pharmacological changes readily visible, is possibly adopting the hopeless position that Dr. Boshes has in regard to histamine therapy in multiple sclerosis. I don't feel on the basis of my experiences that the situation is quite so hopeless. As you know, psychotherapy is inherent *in all medical procedures. There is no justification for allowing a technique to be untried merely because the possibility of psychotherapy is present.* Between Dr. Jonez and myself there are about 100 cases which have been treated by this method.

I should like to point out that there are no *rigid* criteria which can immediately be employed as to whether a drug is efficacious or not. I have had the good fortune to work with Dr. Brickner in New York, and although he is vigorous in his refusal to accept the *final value* of histamine therapy *without further experiment,* I do feel that he is more optimistic in the value of testing various drugs, including histamine, under appropriate conditions.

There is an idea that if you wait long enough in multiple sclerosis, you will certainly get a remission. Neither Dr. Jonez or myself wait for remissions; we think that is too dangerous. In the last six to eight months, with the fairly large number of patients under home and out-patient therapy, there have been no marked relapses, if any, in this group. On the other hand, there have been some unexplained phenomena. For example, in patients on home therapy for about six months, a certain amount of lassitude may set in. They are then removed from histamine therapy for a week or two with a remarkable increase of energy.

I should like to ask Dr. Jonez if he has made any physiological observations on the blood. Does the electrophoretic method form deposits? I believe that it does. I have detected secondary flushes following electrophoretic therapy. On the other hand certain other patients do not flush easily. I do not know why.

CHAIRMAN WITHERS: I am breaking a few rules about the minutes that we are using for these talks because this is an important paper and because there is a great deal of interest in it. Is there anyone else who wants to add to the general discussion?

DR. ROBERT J. BRENNAN: With all due respect to the neurologists, I am just a country boy trying to get along in this work, and I think a lot of allergists take the same attitude toward this histamine treatment that a lot of general practitioners take against allergy. If we are going to take that attitude toward histamine treatment, that is the same attitude we will get from the general practitioner toward allergy in general.

One important point that Dr. Jonez brought out is that you have to treat these patients for a long time. Every once in a while some doctor will call up and say he has Mrs. So-and-So in the hospital and that she will be in there for a week, and he wants to know if we will treat her for multiple sclerosis. You can't treat a patient that way. If you are not going to be able to treat them for a couple of months, you may as well not start. That is the way I feel about it.

As to what eventual good you can do the patient, it is hard to say. Recently I had two patients start treatment about the same time. One was a surgical nurse who had been incapacitated a very short time. We treated her about five times a week with the intravenous method, and in about two months she had a very nice remission and has gone along very well on subcutaneous treatment.

The other case was a man who had the disease fifteen years at least—fifteen years that he knew about—and at the time we started treating him he was practically bed-fast. After two and a half to three months of treatment, he is now able to move

about and drive his own car, and he can talk so that everyone can understand him, whereas originally he was very hard to understand. He is now, as he states it, about seven years better than he was when he started.

He wants to know how long we should keep this up. The way I feel about it is he should just keep it up as long as we can do him any good. This is a sort of hobby with me, and I would advise anybody else to kind of look at it as a hobby, too, because most of these multiple sclerosis cases have been incapacited so long that if you get back the cost of your materials, you will probably feel like you are doing pretty well. You don't expect to make any money on them.

CHAIRMAN WITHERS: Is there any more discussion?

DR. R. J. MARTOCCIO: I am in no position to discuss the papers of the previous speakers, but I do like to emphasize the method of Dr. Abramson.

If you have struggled with some of these patients, you will appreciate what Dr. Abramson's treatment means to you. I had struggled with intravenous therapy, and when Dr. Abramson's method came along, I was able to instruct my mother and one of the members in our family on the use of this therapy in the case of my brother who suffers from multiple sclerosis. It is a very simple method and can be used several times a day. You can teach any member of the family how to use this therapy. Personally, I think this is one of the most important advances in the treatment of multiple sclerosis.

CHAIRMAN WITHERS: I guess we will have to stop this now. Dr. Jonez, will you end the discussion?

DR. JONEZ: I will only take a few moments to end this discussion, as we have already far exceeded our allotted time. First, in reply to Dr. Abramson's question regarding histamine blood levels during intravenous and iontophoresis histamine therapy. I know of no way to determine histamine blood levels during either of these methods of medication. In talking with Dr. Ethan Allan Brown this morning on this subject, he stated, "While histamine was being injected intravenously in one arm, blood can be drawn from the opposite arm, and this drawn blood will be perfectly normal, containing no histamine at all." However, we did discover a method of gauging the histamine effect on the blood with reference to the time the effects lasted. We found that in the blood oxyhemoglobin reached a saturation point very shortly after histamine was administered by either method. Following iontophoresis therapy, the increase in oxyhemoglobin lasted in diminishing amounts for about seven hours. By the intravenous method, the oxyhemoglobin level of the blood reached normal in about two hours. This is some indication as to the length of the effectiveness of the two methods of administration of histamine. This increase in oxyhemoglobin also explains the marked blood pressure drop spoken of by Dr. Abramson and the increased metabolic rate during intravenous histamine administration described by Dr. Horton in a paper several years ago.

I do not know whether this increase in oxyhemoglobin has been noted by other workers or not. We have not been able to find any report in the literature on this phenomena. I would like to ask Dr. Horton if he had observed this change in the blood during histamine therapy.

DR. HORTON: Yes, we have made this same observation.

DR. JONEZ: As to Dr. Boshes and our other neurological friends, I feel, as Dr. Horton expressed himself several years ago, that the neurologists have spent many years, in fact over 100 years, in this search, and all the hope and promise that

they have been able to give these poor unfortunate suffers was "Get yourself a crutch, then a wheel chair, and after that the bed." We, as allergists, are merely trying to do something to lessen the progress of this disease and help these people, and we do help them.

Dr. Boshes spoke about curare in reference to the work done on twelve multiple sclerosis cases at Cook County Hospital. I call his attention to the fact that the preparation of curare used there is an entirely different one from the d-Tubocurarine we use. We have had several cases come to our clinic who had received the curare spoken of by Dr. Boshes without any noticeable effect before coming to us. When given the d-Tubocurarine used in our clinic, they responded in the same manner that the rest of our cases did. After all, Schlessinger reports the same findings in over 400 cases of various spastic conditions that we found in our 152 cases of multiple sclerosis. He uses the same product of d-Tubocurarine that we do. I think our combined more than 550 cases overshadow the work at Cook County Hospital spoken of today.

As a matter of fact, this preparation certainly does quickly relieve spasticities in all parts of the body. However, should it only give these people a dry bed to sleep in, its use is most assuredly worthwhile.

COTTONSEED PROTEIN VS. COTTONSEED OIL SENSITIVITY

(Continued from Page 14)

2. The refining processes of cottonseed oil diminished the atopen content of the oil slightly, but did not destroy its active principle.

The author wishes to express his appreciation to Dr. Matthew Walzer for his many criticisms and helpful suggestions in the above investigation.

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A STANDARDIZED PATCH TEST

LOUIS SCHWARTZ, M.D.
Washington, D.C.

JADASSOHN devised the patch test in 1895 for the purpose of diagnosing contact dermatitis. At that time there was not the clear distinction which we now make between primary skin irritants and sensitizers.

A primary cutaneous irritant is an agent which will cause dermatitis by direct action on the skin at the site of contact if it is permitted to act in sufficient intensity or quantity for a sufficient time. A primary irritant acts locally by direct chemical, physical or mechanical action.

A cutaneous sensitizer is an agent which may not cause demonstrable changes on first contact, but may effect such undemonstrable changes in certain individuals that after five to seven days or more, further contact on the same or other parts of the skin will cause dermatitis. A cutaneous sensitizer acts systemically through the body fluids.

It is obvious that patch tests with known primary irritants are not diagnostic, unless the primary irritants are so dilute as to have lost their irritant properties, whereas patch tests for diagnostic purposes can be performed with any agent which is not a primary irritant and with which the patient has come in contact. Primary irritants may also be sensitizers, as for instance formaldehyde and the alkaline bichromates. The sensitizing powers of substances vary, some of them being capable of sensitizing a large proportion of those exposed and some only a very small percentage; however, the sensitizing potential of each substance is directly proportional to the amount of the chemical and to the time it remains in contact with the skin.

The resistance of the skin of different persons and of even different portions of the skin of the same person varies to the action of both primary irritants and sensitizers. Where the reactive tissue of the skin is covered with many layers of cornified cells, it requires large quantities of primary irritants, or longer contact, to reach reactive tissue, and such a skin will not be sensitized as readily as a skin the reactive tissue of which is nearer the surface.

Individuals also vary in degrees of sensitivity irrespective of the thickness of the skin. Some are so sensitive that the mere presence of the allergen in the same room will cause them to itch. I've seen workers who were so sensitive to some chemicals with which they had worked, that even going into the vicinity of the factory caused them to break out in a rash. Then again, the degree of sensitivity may vary from time to time.

The patch test as used heretofore has not been standardized. Different dermatologists would use different techniques of applying the patch test.

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Dr. Schwartz is an Honorary Fellow of The American College of Allergists.

Some would saturate a piece of blotting paper of indefinite size and apply it to the skin. Others would use various sized pieces of various plies of surgical gauze, containing indefinite amounts of the liquid or powdered solid. As a result it was often found that one dermatologist could not duplicate or substantiate the results obtained by another.

We know that the reaction to a patch test depends on (1) the degree of sensitivity of the patient, (2) the concentration of the substance applied, (3) the amount of the substance applied per square centimeter of skin, and (4) the length of time that it remains in contact with the skin.

In performing a diagnostic patch test, we have heretofore controlled the time the patch has remained on the skin, and in some instances we have known or controlled the concentration of the irritant; but we have not definitely controlled the amount of the irritant nor the area of skin to which it was applied.

Because of this, the results by different observers have varied. Some, using small amounts of allergens on larger areas of the skin, have obtained slight or no reactions on patients who showed marked reactions when larger amounts were used by others.

All these facts have led to devising a method of patch testing by which definitely known amounts can be applied to a constant area of skin, for definitely known periods, all of which can be recorded and stated when the reactions are read.

The proposed standard patch consists of (1) a square piece of flannel measuring 3 sq. cm. which becomes saturated with 0.2 c.c. of a liquid, (2) a pipette graduated so that measured amounts varying from 0.05 to 0.2 c.c. can be applied to the flannel, (3) a square piece of uncoated regenerated cellulose 1 to 1½ inches on each side, used for insulation, and (4) a piece of elastoplast of a special shape measuring 3 inches across the diagonal. The piece of cellulose is adhered to the center of the elastoplast and the piece of flannel is attached to the center of the cellulose. If it is desired to patch test with a liquid the concentration of it must be known and a definite amount placed on the flannel. The patch is then applied to the skin, and permitted to remain on for a definite period.

The result is written as follows:

Substance	*Site*	*Concentration*	*Solvent*	*Amount*	*Area*	*Time*
Amm. Thioghyco.	R. forearm	5%	Water	0.15 c.c.	3 sq. cm.	24 hrs.
Amm. Thioghyco.	L. forearm	10%	Water	0.15 c.c.	3 sq. cm.	24 hrs.

Reaction — ++ Delayed Reaction + —

The relative sensitivity of different subjects can also be determined by placing patches of similar concentration on them and noting the degrees of the reactions.

Thresholds of sensitivity can be determined by placing various amounts of the same concentration or the same amount of various concentrations on the same subjects.

The relative sensitizing powers of chemicals may be determined by placing patches of similar concentrations of each chemical on several hundred subjects, allowing them to remain on for the same definite period and repeating the procedure ten to fourteen days later and noting the number of subjects sensitized by each substance and the degree of the reactions.

The sensitizing properties of solids can be determined by dissolving definite amounts in a suitable solvent, applying 0.2 c.c. of the solution to the 3 sq. cm. piece of flannel and allowing the flannel to remain on a porcelain or glass surface until the solvent evaporates. This procedure will deposit on the flannel an evenly distributed known amount of the substance to be tested. The dry patch can then be applied.

If it is desired to use larger amounts of the sensitizing chemical, higher concentrations of the solution can be used; or if this is not possible, after the solvent has evaporated from the flannel, 0.2 c.c. of the solution can be reapplied to the flannel and the solvent can again be permitted to evaporate, thus leaving on the flannel double the amount of solid. This procedure can be repeated as often as desired, tripling, quadrupling, et cetera, the amount of solid dispersed on the flannel.

Ointments can be tested by spreading definite amounts over the surface of the 3 sq. cm. piece of flannel.

The kit consists of the prepared patches and a graduated pipette or dropper which permits the application of the desired amount of liquid to the flannel. (A hypodermic syringe having a small calibre may also be used to measure the amounts of liquid.) If larger pieces of flannel are desired, they can be cut, but the areas of the pieces must be known and recorded so that results can be evaluated.

When liquids are used for patch testing, they sometimes spread, covering the area of skin under the insulating cellulose; this happens if pressure is applied on the patch at the site overlying the wet flannel. Therefore, in applying the patch, pressure over this site should be avoided by pressing on the tabs at the corners of the patch in order to make it stick, rather than pressing on the center. However, the liquid does not spread beyond the cellulose insulation because the plaster adhering to the skin at the borders of the cellulose prevents spreading.

The adhesive is spread on a square piece of elastoplast and the patch cut so that it has a tongue at each corner, on which slight traction can be made in applying the patch. The procedure practically gives the patch the property of a two-way stretch.

SUMMARY

A new patch test device is described which permits the performance of comparable and standard patch testing.

915 15th Street N. W.

SKIN TESTS WITH STEROID HORMONES IN ALLERGIC DISEASES

MARY-KATHARINE HAJOS, M.D.
Budapest, Hungary

THE publication by Doctors Baer, Witten and Allen, "Skin Tests with Endocrine Substances," in the May-June, 1948, issue of ANNALS OF ALLERGY, recorded dermatological cases. We performed the same tests according to Zondek and Bromberg's method for well over a year at the Medical Department of the Apponyi Policlinic, Budapest. As the majority of our patients suffered from allergic asthma, I would like to add our own results in the study of endocrine allergy.

Hormone solutions in olive oil vehicle (prepared for us in the G. Richter chemical laboratories, according to Zondek's indications) were as follows: desoxycorticosterone acetate, progesterone, pregnandiol, estrone, testosterone, androsterone. Aqueous solutions of glanduantin and insulin served for testing only in case of evident sensitivity with these substances.

Subjects for our tests were carefully chosen from among allergic patients, whose allergic manifestations were closely related to the sexual cycle, i.e., premenstrual tension, menstruation, pregnancy, preclimax, climax. The total number of cases thus tested amounted to 107, out of which twelve adults—males and females with nonallergic complaints—and four children served as controls to check the specificity of our results.

Diagnosis of allergic subjects with suspected hormone sensitivity was as follows:

Total number of suspected cases: 79 female, 12 male.

Bronchial asthma	63
Urticaria, eczema	13
Pruritus	2
Hyperthyroidism + asthma	2
Obesity	6
Climax	4
Keratitis rosacea	3

Positive reactions were as follows:

	Female	Male
Progesterone	25	12
Pregnandiol	11	
Estrone	10	
Testosterone	8	2
Androsterone	7	4
Desoxycorticosterone	6	
Neohombreol		1

Olive oil and cholesterine had been used for controls, with positive results twice with olive oil, and once with cholesterine, without hormone sensitivity. Control cases never proved to have positive reactions. The evaluation of male subjects has to be treated carefully, as results were neither characteristic nor convincing. The only conclusion we attempt to reach is the observation of sensitivity in male subjects under forty years of age to male hormones and over forty, to female sex hormones.

Other observations are as follows:

1. In cases of allergic manifestations associated with the sex cycle, hormone testing proved to be more or less positive.

2. Hypersensitivity to various hormones at the same time is, regardless of the sexual character of the hormones, in question. Simultaneous positive reactions with progesterone and androsterone, testosterone and estrone—as occurring most frequently—may be explained by the well-known fact that testosterone may possess progesterone-like properties, while progesterone occasionally simulates androgenous effects.

CASE REPORTS

Case 1.—Mrs. G. I., aged thirty-four, had been treated previously with glandubolin (Estrogenic substance, sec. G. Richter) because of menstrual disorders. She developed severe urticaria after the fifth injection. The eruptions persisted about a week after administration of the hormone. When her urticaria subsided, and menstrual complaints as regards irregular periods did not improve, another hormonal treatment, first with syntestrin, then with glandubolin, was attempted. Following the first injection of glandubolin, urticarial eruptions flared up. She was then hospitalized and treated first with the usual methods. When her urticaria had subsided, we performed our hormone testing, with the result of sensitivity to estrone and pregnandiol. Intradermal tests with glandubolin elicited severe local and generalized symptoms. Treatment was started with small doses of estrogenic hormone, with complete disappearance of symptoms after a two-month course.

Case 2.—Mrs. K. B., aged twenty-seven, had her first eczematous symptoms after an abortion two years ago. Since then her periods have been irregular, and she has noticed intermenstrual flare-up of eczema. As checked by hormone-level calculations, we found the exacerbations to occur approximately at the time of ovulation. The hormone tests showed sensitivity to all female sex hormones. Treatment with small doses of estrogenic hormone improved her complaints.

Case 3.—Mrs. H. H., aged fifty-seven, came with ocular allergic complaints. Hormone testing gave positive results with estrone. She had previously undergone a treatment of syntestrin and glandubolin. Small doses of these hormones improved her symptoms.

Case 4.—Mrs. P. J., aged fifty-three, had been treated for bronchial asthma for twenty-two years. Her menstrual history disclosed that she had never menstruated at all. Testing her with hormones, she presented elective progesterone sensitivity of a very high degree. The local reaction subsided for over a month, and flared up during several cycles substituting menstrual cycles. Treatment with small doses of proluton improved her asthmatic manifestations.

We still continue our studies in endocrine allergy, but in our subsequent tests we are going to emphasize the correlation of hormone sensitivity to hormone levels in the organism and changes of the vasomotor nervous system. We wish to extend our investigations in tests for thyroxin-sensitivity as well.

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THE PARENTERAL USE OF NEO-ANTERGAN

A Clinical Study

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NEO-ANTERGAN, an effective histamine antagonist, has been shown to possess antihistaminic, anti-anaphylactic and wheal-reducing properties. Comparative clinical studies of the antihistaminic activity of various drugs administered orally revealed Neo-Antergan to be equal to or greater than most histamine antagonists.[2,3,4,5,6,8,11,12,13,14,16,17] Since the parenteral administration of Neo-Antergan has not been reported in the human, it was deemed advisable to investigate and report its clinical effect. Neo-Antergan Maleate,* a brand of pyranisamine maleate (N'-p-methoxybenzyl-N', N'-dimethyl-N-a-pyridylethylenediamine maleate), was used throughout the experiment.

PROCEDURE

Neo-Antergan was administered to a group of 138 patients during the summer and fall of 1948. The series comprised patients suffering from seasonal and perennial hay fever, asthma, urticaria, atopic dermatitis, migraine, and allergic conjunctivitis. The drug was administered either by the intravenous or intramuscular route. Each cubic centimeter contained 10 mg. of Neo-Antergan Maleate. In order to determine the optimum dosage the drug was administered in amounts varying from 2 to 15 mg. The average dose was 4 to 5 mg. The patients were not selected and consisted of cases obtained from private practice and clinic. There were fifty-seven males and eighty-one females, ranging from eight to sixty-seven years of age.

Neo-Antergan was used concurrently in patients receiving coseasonal desensitization and in those cases that did not obtain 50 per cent relief from the perennial or preseasonal method of desensitization. It was administered parenterally during the pollinating season at the time the patient was manifesting symptoms, regardless of the concentration of the pollen in the atmosphere. Normal saline, a placebo, was used as the control. Patients claiming relief from Neo-Antergan had normal saline substituted and its effect noted. The relief obtained was based upon the patient's subjective statements, and corroborated by the findings in the eyes, nose and chest.

In order to determine the time that elapsed for the drug to take effect, the duration of relief, and the side reactions, each patient received one to six injections. Laboratory studies included complete blood count, urinalysis and electrocardiogram. Urine specimens and blood counts were taken before treatment and two to four times during the course of the survey.

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*Furnished through courtesy of Merck and Co., Inc., Rahway, N. J.

TABLE I. TYPES OF ALLERGIC CONDITIONS RECEIVING NEO-ANTERGAN

Seasonal hay fever	
1. Co-seasonal	41
2. Perennial and preseasonal with less than 50% result	31
Perennial allergic rhinitis	28
Bronchial asthma	14
Atopic dermatitis	6
Urticaria and/or angioneurotic edema	12
Migraine	4
Allergic conjunctivitis	2
Total	138

TABLE II. SYMPTOMATIC RELIEF PRODUCED BY NEO-ANTERGAN

Diagnosis	No. Cases	No. Improved	% Improved
Hay fever	72	46	63.8%
Perennial allergic rhinitis	28	18	64.0%
Bronchial asthma	14	4	28.5%
Atopic dermatitis	6	2	33.0%
Urticaria and/or angioneurotic edema	12	8	66.0%
Migraine	4	1	25.0%
Allergic conjunctivitis	2	0	0.0%

RESULTS

The intravenous method produced severe drowsiness, almost to the point of stupor. Other patients complained of pressure symptoms in the chest, perspired freely, became dyspneic and developed wheezing respirations. The intravenous method was therefore discarded in favor of the intramuscular route.

The relief of symptoms from the parenteral administration of Neo-Antergan, usually occurs within ten to thirty minutes. The duration of relief varies from one to ten hours, with an average of four to five hours. Table II indicates the symptomatic relief obtained following the parenteral administration of Neo-Antergan.

The best results were obtained in patients suffering from seasonal and perennial hay fever and urticaria. In the hay fever group it relieved the sneezing, itching of the eyes and nose, severe rhinorrhea, and cleared the nasal passages. Substitution of a placebo in the form of normal saline for the antihistaminic drug failed on repeated occasions. Upon reintroducing Neo-Antergan, the patient obtained symptomatic relief.

A favorable response was obtained in urticaria and angioneurotic edema. Its antipruritic effect was fairly rapid and pronounced. The massive swellings diminished in size and at times disappeared. The rapidity of relief was equivalent to that of epinephrine, without producing the palpitations, tachycardia, pallor and nervousness. The effect of Neo-Antergan at times was more prolonged than epinephrine, and its sedative effect an added point in its favor. Upon discontinuing the drug, the symptoms recurred, and were once again relieved with its re-introduction. In a proper evaluation of results, it must be remembered that acute urticaria is a self-limited disease. In chronic urticaria, the lesions tend to recur.

The results in bronchial asthma were somewhat disappointing. In two patients, the asthma was precipitated or aggravated by the administration of Neo-Antergan. In those cases of hay fever that progress to asthma, Neo-Antergan also fails to relieve the distressful respiratory symptoms.

Atopic dermatitis does not respond favorably to Neo-Antergan. The antipruritic effect was noteworthy, but since the syndrome continued unabated the results were recorded as unimproved. Its importance is in the sedation that is afforded the patient at night, which prevents the trauma and secondary infection incident to the scratching.

Only one patient with migraine improved. The remaining three were unaffected. Two patients with allergic conjunctivitis did not respond to parenteral Neo-Antergan. While the number of cases is too small to warrant conclusions, the results are consistent with those of other observers.

Urinary analysis revealed no abnormalities. Hematologic determinations were all within normal limits. The electrocardiograms revealed no abnormal cardiac physiological changes.

Side reactions occurred in thirty-two of the 138 cases. The type of side reaction is listed in Table III.

TABLE III. SIDE REACTIONS WITH NEO-ANTERGAN

Side Reactions	No. of Cases
Drowsiness	39
Dizziness	7
Dry Mouth	5
Dry Nose	4
Tinnitus	2
Weakness and Fatigue	2
Abdominal Cramps	1
Asthma	2

A total of sixty-two undesirable effects were noted in the thirty-two cases. Drowsiness seemed to occur far in excess of the other untoward reactions. One patient who was driven to her place of employment was found asleep at her typewriter. Other reactions noted are dizziness, dry mouth and nose, tinnitus, weakness and fatigue, abdominal cramps, dyspnea and aggravation or precipitation of the asthmatic attack. The potential danger of these reactions, particularly the soporific effect, becomes quite apparent. The undesirable effects seem to appear more frequently when Neo-Antergan is given intravenously. The side reactions increase in proportion to the amount of the drug that is used.

DISCUSSION

The parenteral administration of Neo-Antergan is only a palliative procedure. It may be used concurrently in those patients not receiving adequate relief from specific therapy. Clinically, Neo-Antergan is a valuable adjunct in the symptomatic treatment of hay fever. This procedure, however, will not prevent the progression of hay fever to the asthmatic state. The results obtained are comparable to those of Bernstein,[1] who found that oral Neo-Antergan relieved 65 per cent of patients suffering from hay fever.

The results obtained in urticaria are in accord with those of Waldbott.[15] Koelsche[10] reported 74 per cent relief in patients having hay fever and asthma. However, only one-third of the 74 per cent obtained relief of the associated asthma. Waldbott also states that asthma responds less favor-

ably to the antihistaminic drugs than does hay fever. He therefore suggests that there is a more pronounced antiwhealing than bronchial inhibiting effect. Henderson and Rose[9] report similar results in migraine with Pyribenzamine. Friedlaender and Friedlaender,[7] using Pyribenzamine, report failures in migraine and vernal conjunctivitis.

Many patients suffering with some form of allergic disorder are not benefited by or cannot tolerate oral medication. It is in this group that the parenteral administration of Neo-Antergan is of distinct value. Its duration of action as compared with epinephrine is a point in its favor. The undesirable tachycardia, palpitation and nervousness produced by epinephrine is avoided. The sedative action of Neo-Antergan may be desirable at times. It does not however warrant replacement therapy of epinephrine, the iodides, aminophylline or the sympathomimetic drugs.

The incidence of relief and the side reactions were compared with the results of other observers using various antihistaminic agents. The degree of relief and the percentage of side effects tend to run parallel with the other histaminic antagonists. The vagaries of the allergic state at times made it difficult to properly evaluate the duration of relief.

SUMMARY

1. Neo-Antergan, an antihistaminic drug, was administered intravenously and intramuscularly to a group of 138 cases.

2. It was found to be very effective in the relief of symptoms of seasonal hay fever, perennial allergic rhinitis and urticaria.

3. It is of questionable value in bronchial asthma, atopic dermatitis, migraine and allergic conjunctivitis.

4. Side reactions occurred in 23 per cent of the cases.

5. Urinalysis, blood counts and electrocardiograms were relatively normal.

6. The incidence of relief tends to run parallel to the other antihistaminic drugs, as reported by various investigators.

7. It has an apparent potential advantage in that it may be administered parenterally.

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ALLERGIC TOXEMIA AND FATIGUE

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IN 1927 allergic toxemia in children due to pollen was reported by Kahn.[1] Soon after, the writer realized that food allergy was a much more common cause and in 1930 published a paper on Allergic Toxemia* due to Food Allergy.[5] Fatigue, weakness, lack of energy and ambition, drowsiness, loginess, bodily aching, depression, irritability, fever, chilling and night sweats were reported in varying combinations and degrees. Since then we have continued to report these symptoms from food and less so from pollen allergy. In 1936[6] statistics on twenty-nine relieved patients were published. Moreno in Buenos Aires has written five articles on the toxemia[3] since 1940, and one additional excellent article has appeared in American literature by Randolph[4] in 1945. Recently Mariante[2] has reported on this syndrome.

All other possible causes of fatigue and these other symptoms must be ruled out, including infections, new growths, metabolic, vascular, blood and endocrine disturbances and mild or definite insanities. Today there is a vogue of ascribing fatigue and related symptoms to "benign nervousness" or psychosomatic causes, as found in articles by Allan, Portis and others. When present-day and traditional examinations and tests have been negative, or treatment based on positive findings has failed, I agree with Randolph that this diagnosis is not justified unless allergy also has been excluded by proper and adequate study. The demonstration of other diseases or pathologic conditions, moreover, does not exclude concomitant allergic toxemia. Without the recognition of this allergy, patients unjustifiably may be stigmatized as psychoneurotic or even psychotic, often being left to cope with their disabling symptoms alone.

Fatigue and weakness due to allergy may be most evident in the mornings, even after a long night's rest or sleep. Patients hate to get up or may find it difficult to awaken. Often this fatigue continues throughout the day. One patient said, "I'm so tired I wonder how I get through the day." Another stated, "I get tired and achy doing nothing." Some have to lie down most of the time. This fatigue may increase in the late afternoon and evening, causing sleep, drowsiness and inability to concentrate mentally after dinner. With the control of the allergy, these results disappear. One relieved patient stated that now she is anxious to work, formerly having forced all mental and physical effort. She can accomplish much at home, even in the evening, which she "hasn't been able to do for twenty years."

Loginess, mental confusion and drowsiness probably due to cerebral allergy often are associated with the fatigue. This leads to inefficiency, impaired accomplishment and ambition. These symptoms, along with irritability, tenseness, depression and at times emotional instability, produce

*Drug allergy also produces many of the symptoms of this allergic toxemia and fever.

TABLE I. ALLERGIC TOXEMIA AND FATIGUE IN 70 PATIENTS*

		Per cent
Average age	42 (10-70)	
Male		28
Female		72
Duration of toxemia	9.4 years (1-40)	
"Toxic symptoms"		
Fatigue		94
Not rested on arising		57
Lack of energy		66
Aching in joints		47
Aching in muscles		36
Aching in chest		10
Loginess, listlessness, drowsiness		37
Disability in concentration		27
Confusion		17
Depression		30
Irritability		20
Nervous tension		34
Emotional instability		6
Insomnia		11
Fever		10
Night Sweats		3
Chilling and gooseflesh		3
Tachycardia		10

*All of these patients were relieved of their various symptoms by the elimination of allergenic foods. All other possible causes were studied by the writer or by referring physicians. Several patients had been to 6 to 12 and one to 18 physicians. Psychiatric and psychosomatic study and treatment had been resorted to by 8 patients.

Many other patients with other various manifestations of food and inhalant allergy had mild or moderate fatigue and other symptoms of this toxemia. Moreover many patients with severe sick headache preceded or associated with fatigue and exhaustion were not included. Finally the many patients with ulcerative colitis, due in our opinion fundamentally to food, and at times to pollen allergy, in whom marked exhaustion, fatigue and depression and other symptoms occurred, were omitted.

changes in personality that may be recognized by the patient but are uncontrollable. When these allergic symptoms occur in children, their true cause usually is overlooked. Thus a boy of two and one-half years was seen two years ago because of "head colds" with listlessness, drowsiness and lack of energy since birth. These symptoms had been exaggerated every week or two with fever up to 104°F. for two to four days. Drowsiness or sleep often continued for three to four days. In the second year fever decreased but perspiration for days at a time developed. Physical and mental activity was retarded. "He just sat. He never wore out his shoes." Doctors, including a psychiatrist, opined that he was subnormal mentally and probably would never go to school. All of these symptoms, except slight drowsiness every few weeks, have been absent with an elimination diet in the last twenty months. He is energetic and alert. Shoes are worn out in two months.

Other children become sullen, obstinate, incorrigible, have bursts of temper or cannot adjust themselves to other children. School work suffers. With the control of allergy a normal personality gradually is established and maintained.

Thus a girl of seven years had had "sinus attacks" every four to six weeks for four years, associated with cough and fever from 101° to 105°F. for a week or more. She was constantly lifeless and unwilling to play, saying she felt "like a rag doll." Nervousness and fatigue interferred with school work. "She frequently was naughty, had tantrums, and was impossible to control." Her appetite was poor. She refused to eat for most of her six years. Doctors had been consulted with no benefit.

TABLE II. ALLERGIC TOXEMIA AND FATIGUE IN 70 PATIENTS

Manifestations of allergy other than toxemia	Per cent
Gastrointestinal allergy	63
Headache (including nuchal pain)	50
Eczema	10
Hives and swellings	16
Hay fever	9
Nasal allergy	34
Bronchial asthma	6
Urogenital allergy	4
Epilepsy and petit mal	3
Family history of allergy	
Bronchial asthma	23
Nasal allergy	9
Hay fever	11
Eczema	7
Hives and swellings	7
Headaches	17
Gastrointestinal symptoms	19

With the cereal-free elimination diet, improvement was noted in two weeks, "and she was a different child in four weeks." Normal energy and a "spring in her step" developed. She ate all the time, taking second helpings, eating between meals and saying "I am sure hungry," instead of "I don't like that old stuff." "She attends school all day, comes home full of energy, rakes leaves, climbs trees and keeps going until ten o'clock at night." Nervousness and a tendency to crying ceased. She has been at the top of her class and has been chosen to represent her class in a school play.

Dreams, nightmares and restlessness during the night may occur. Insomnia, especially on retiring or after 1:00 to 4:00 a.m., may be present in infants and children and especially in adults.

Aching and soreness in the joints, tendons and muscles often result from allergic reactivity, especially from foods. At times this is confined to a few joints or to limited areas such as the low mid-back, the nuchal or shoulder areas or extremities. Food allergy along with bacterial and other allergies needs consideration as one cause of incipient or established rheumatoid arthritis, the allergic nature of which is indicated by the collagen and other tissue and joint changes described especially by Rich. Several encouraging results in rheumatoid arthritis as well as in chronic or recurrent tendo-synovitis have justified our study of food allergy along with its other allergic and generally considered causes.

At times, fever, chilling, and sweating apparently occur in varying degrees from food allergy. Resultant vascular allergy probably accounts for the hypotension and tachycardia which often arise from food and other allergy. Food allergy, together with inhalant, bacterial and the demonstrated drug and serum allergies, also need to be studied in periarteritis nodosa, the allergic nature of which is recognized.

All of these symptoms may vary in degree. As in other manifestations of food allergy, such as asthma or recurrent headaches, this toxemia may occur in cyclic attacks. Usually it is persistent, exaggerated at regular intervals especially in women during their periods. Because of the beneficial effect of the summer and also inland, dry areas on food allergy, long reported by the writer, allergic toxemia may decrease in these months and in such regions. Exaggeration of symptoms during the spring, summer and

TABLE III. ALLERGIC TOXEMIA AND FATIGUE IN 70 PATIENTS

	Per Cent
Skin testing	
Pollens	20
Animal emanations	11
Dusts	10
Miscellaneous inhalants	11
Foods	21
Roentgen ray studies of gastrointestinal tract negative in	27
Roentgen ray studies of gall bladder negative in	23
Stomach analysis negative in	16
Achylia in	4
Positive dietary history	40
Causes	
Food allergy	93
Food and pollen allergy	1
Pollen allergy alone	6

fall occurs in toxemia due to pollen allergy. Other manifestations of allergy, especially cerebral, gastrointestinal, and nasal occur in these patients, varying in numbers as shown in Table II.

PATHOGENESIS AND PATHOLOGY

The pathogenesis of this syndrome is not known. Randolph[4] has reported atypical mononuclear cells resembling those found in infectious mononucleosis in patients with allergic toxemia. Other evidence of systemic disturbance is lacking. Chronic allergy, especially to foods, does not produce recognized changes in the blood except leukopenia after ingestion of allergenic foods, reported especially by Vaughan. Eosinophilia is not usual. The sedimentation rate has been increased in some of these patients in the absence of any demonstrable cause other than chronic food allergy.

The symptomatology depends on the tissues affected by the allergic reactivity. Vascular allergy is known to produce vascular inflammation, increased permeability and local edema. The possibility of collagen disturbances, the maximum evidence of which has been demonstrated by Rich and others in periarteritis nodosa, has to be considered in patients with severe long standing allergic toxemia.

Information from tissue biopsies in these patients would be of great interest, but the good prognosis in co-operating patients does not justify this study. The absence of fatalities in these patients allows no post-mortem examinations.

DIAGNOSIS AND CONTROL

Food allergy should be suspected when these symptoms of toxemia are present, and especially if other manifestations of food allergy, enumerated in Table II, are evidenced in the history.

A dietary history of dislikes or disagreements for foods suggests but does not affirm allergy as a specific cause. Specific questions should be asked, such as, "Do you like milk, eat eggs, fish or fruit?" Thus patients may state that they hate milk, or that it is a poison, or that it causes vomiting, or pain in various parts of the abdomen, or asthma. One patient found it made her "sick all over and tired for a week." Another was certain that

fatigue developed in two or three hours from milk even in very minute amounts. Egg, fish or fruit allergy often is evidenced in the history. One of my patients has found that grapes as such, or in wine or even vinegar, produce allergic toxemia.

Skin testing is of little help. When the patient knows that immediate and severe reactions occur to specific foods, reacting bodies may be in the skin, as shown by the positive scratch reactions and by a positive Prausnitz-Kustner reaction. But when clinical symptoms from food allergy are delayed for a few hours or are accumulative, appearing in one or two days after the ingestion of the food, the skin reaction usually is absent. Too often, small or even definite reactions to foods, especially by the intradermal method, indicate past or potential allergy or are nonspecific. Positive skin reactions, moreover, must be confirmed by reproduction of symptoms in the symptom-free patient from the ingestion of the specific food.

Thus diet trial becomes our most important diagnostic measure. In some patients the exclusion of foods indicated by dietary history or by large scratch reactions gives relief. This usually fails, especially when symptoms are due to the cumulative type of food allergy. This has justified the use of our elimination diets with their detailed menus and recipes for bakery products.

The writer's cereal-free elimination diet[7] usually is ordered for the initial study of possible food allergy in these patients. If improvement is not evident in two or three weeks, then the fruit and cereal-free elimination diet may be utilized. This fruit-free elimination diet, moreover, is used for initial diet trial if the dietary history indicates probable fruit allergy. If no relief develops in another two or three weeks and food allergy still seems likely, a minimal elimination diet may be tried, such as one containing lamb, white potato, tapioca, sugar, noniodized salt and water, with vitamins A and D in a relatively nonallergic form such as Provotal, and calcium carbonate 1/3 to ½ teaspoonsful doses daily. This diet can be prepared to contain 60 to 80 grams of protein and 2,000 or more calories each day. When relief with any of these elimination diets is assured, individual foods are added, one every four to seven days, excluding any which reproduce symptoms. However, if a diet is producing relief of long standing chronic symptoms, especially if chronic tissue changes exist as in allergic arthritis, the relieving elimination diet should be continued for weeks or even months, always with definite assurance that nutrition requirements are being satisfied.

The necessity of absolute exclusion of disallowed foods and the prescribing of the elimination diet with menus and directions so that nutrition and weight are maintained require constant emphasis. It requires more than a few days for the allergens of previously eaten foods to leave the body and especially for the cellular changes resulting from long existent chronic food allergies to decrease or disappear.

Pollen allergy is indicated by history, more successfully by skin testing

than in food allergy, and finally is confirmed by beneficial pollen desensitization. Other inhalant allergy, which at times causes allergic toxemia, as evidenced by reports of Rinkel and others, and by our own observations, requires similar study and treatment, as discussed above for pollen allergy.

If drug allergy is suspected, total or prolonged exclusion is the answer.

For the symptomatic control of the manifestations of allergic toxemia, epinephrine, hypodermically, may be tried. The antihistaminic drugs in our experience will not control the chronic severe symptoms. They help the mild ones, especially those arising in patients on proper diets who unwittingly or against orders break their diets. Histamine therapy rarely is of help. Aspirin or acetamine gives temporary relief. Allergy at times to many drugs and toxic reactions or allergy to the antihistaminic drugs must be remembered.

SUMMARY

Allergic toxemia or fatigue due to food allergy was first reported by the writer in 1930 and since then by Moreno and Randolph.

It produces fatigue, weakness, lack of energy, and ambition, drowsiness, loginess, bodily aching, depression, irritability, restless sleep, insomnia, fever, chilling and night sweats in varying combinations and degree.

Pollen and also drug allergies are less frequent causes.

Food and less often other allergies must receive adequate study along with other possible infections, metabolic, vascular and endocrine diseases, new growths and true psychoses before these patients are stigmatized as psychoneurotics suffering with "benign nervousness." In children this fatigue is often associated with nasal or bronchial allergy, especially from foods, producing recurrent so-called "colds," with or without asthma, and frequently associated with fever and sweating due to food allergy rather than infection.

In adults such fatigue, bodily aching, depression, nervousness, dopiness and the other symptoms of this toxemia may be so active that actual work in business and the home, or efficiency therein, is impossible.

The control of food allergy nearly always depends on the accurate use of trial diets, for which the writer's various elimination diets, as described in the above article, have been of increasing help during the last twenty years.

CASE HISTORIES

Brief summaries of the following cases of allergic toxemia show the varying symptoms of this syndrome which may occur. Other manifestations of clinical allergy (Table II) may or may not be present. Because of space, negative physical and laboratory findings and negative skin reactions to foods and inhalants are omitted.

Case 1.—A woman of twenty-nine years had been fatigued for four years, spending an increasing time abed. She had been nervous, perspired easily and slept poorly. "Just gets weaker and weaker, and yawns all the time." Her tongue was coated;

there was pain and soreness in the left abdomen; hemorrhoids and constipation were present.

Dietary history revealed distention from milk, pain in her abdomen for three to four days from egg, and much abdominal distress from fruits.

With the fruit-free elimination diet it was found that her symptoms were relieved and that milk, egg and all fruits, nuts and spices were necessary to exclude for continued comfort.

Case 2.—A woman of thirty-four years had had fatigue, bodily aching, lethargy, emotional instability, nervousness, irritability and much recent depression for two years. Her fatigue was not relieved even with twelve to fourteen hours of sleep. Tachycardia had been present much of the time. Epigastric distention, belching and heartburn had been present nearly continually in the last year. Constipation had occurred two to three days each week. Eczema of the neck had occurred during two winters.

Thyroid and tobacco had been eliminated through the advice of one physician, and several others had been consulted without benefit.

With the fruit-free elimination diets,[7] symptoms were decreased in two weeks and greatly relieved in one month. In two more months all symptoms, including fatigue, nervousness, tachycardia, indigestion and constipation, were controlled. Weight had increased from 118 to 130 pounds. During the last year this control has continued with the elimination of all fruits and spices, bacon, coffee, pork and no egg or milk as such.

Case 3.—A woman of fifty-nine years had had fatigue, exhaustion and stiffness all over the body for twenty years. The "arthritis" had been severe in the knees, shoulders, lower back and neck, being exaggerated in attacks for days or weeks and increased with exercise. She had pulled herself out of bed for several years. A surgical girdle was worn for fifteen years.

Her arms tired so easily she had been unable even to brush her hair.

Treatment by several doctors including internists had been of no help.

With the fruit-free elimination diet, her symptoms were relieved in two months, and the continued exclusion of milk, eggs, all fruits and spices has been required.

Case 4.—A woman of thirty years, after return from the Philippines seven years ago, developed fever up to 103° to 104°F. for one to four weeks, every six months, increasing to every three to four months. In the last two years fever from 99° to 101°F. had been present daily. Weakness, exhaustion, dopiness, restless sleep and depression had continued, varying in degree. Generalized aching especially in the hands, fingers and feet had occurred. Headache, especially in the back of her neck and eyes, had recurred every two to four weeks, often associated with nausea and vomiting. Blocking and buzzing of the ears, congestion and tingling in the nose and a lump in the throat had been frequent.

The dietary history revealed a dislike for egg, pork, and fish and fruit increased many of her symptoms.

Her mother had recurrent headaches.

All examinations including studies for known causes of persistent fever had been done by several physicians with no benefit from any treatment.

Skin testing revealed no reactions to important inhalants or foods.

With the fruit and cereal-free elimination diet, all her symptoms were controlled during a two-month period. It has been found that all fruits, fish and corn must be excluded. Corn produces a severe headache in twelve hours. Fruit produces cramps in thirty minutes and dysentery with a dizzy feeling for one and one-half days.

Case 5.—A man of fifty-seven years first developed aching, soreness, swelling and stiffness in the flexor tendons of the palms ten years ago, with rapid extension to other joints of the fingers, wrists, feet, ankles and elbows. Aching and soreness occurred especially in the mid-thoracic areas of the spine with associated aching around the chest, especially in the cardiac area. The soreness and swelling of the joints had occurred every two to four weeks for five to ten days at a time.

Fatigue, exhaustion, and varying depression had occurred with the above symptoms, increasing in degree throughout the years. He had severe allergic dermatitis from penicillin by mouth and parenterally three times.

Many physicians had sought for foci of infection and gout, hypothyroidism and other possible causes including psychosomatic influences without benefit. The strain of his professional responsibility was blamed.

All symptoms were lessened in inland areas, especially in the summer.

With the fruit-free elimination diet, fatigue, exhaustion, depression and the aching of the body and soreness and swelling of joints were relieved. For continued relief all fruits and spices, squash, pumpkin and milk, as such must be eliminated.

Case 6.—A woman of seventy years was first seen in June, 1946, because of fatigue, generalized aching, weakness and a trembling in her legs, and a "poisoned, slowed down feeling" increasingly in the last ten years. For ten years constipation, distention and a pressure throughout the abdomen, especially in the epigastrium and under the sternum, had increased. At times this distress prevented rest at night, and she feared heart disease. For six months there had been eight to ten watery, nonbloody daily stools with some cramping and much urgency.

Rich, heavy foods, and especially fruits, had increased her abdominal discomfort.

All examinations, including roentgen ray studies of the gall bladder and gastrointestinal tract were negative except for an achylia. Large doses of dilute hydrochloric acid relieved her diarrhea but none of her other symptoms.

With the fruit-free elimination diet, all symptoms of her "toxemia" were relieved in two months. It has been necessary to eliminate all fruits, spices and flavors, milk, wheat and chocolate to maintain control. Though she ate no fruits, her symptoms returned while canning fruits, indicating entrance of the fruit allergens into the body by inhalation.

Case 7.—A man of forty years had had aching and tiredness in the calves for two years. Generalized fatigue and loss of energy had occurred for the last six to eight months, even after nine hours in bed. He forced himself in his work and "wanted to flop in the evening." He had awakened one to three times each night with night sweats. A headache has been present on awakening three to four times a week.

All examinations, including x-ray of his gall bladder, and stomach analysis were negative.

With the fruit-free elimination diet, his symptoms gradually disappeared in five weeks. With the addition of other foods, wheat reproduced his fatigue and aching in the legs. This result has been repeated several times in the last year.

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MERCUHYDRIN SENSITIVITY
Report of a Case

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IN recent years several articles have appeared in the literature dealing with untoward reactions to mercuhydrin and other mercurial diuretics. These reactions have been classified as either toxic or allergic. In the latter group various manifestations have been reported, such as erythematous eruptions, exfoliative dermatitis, urticaria, chills and fever, anaphylactoid shock and even death. Gottlieb,[5] in a recent review of the subject, discussed the allergic nature of these untoward reactions and added one case of his own in a man who received mercupurin and developed generalized urticaria and slight elevation of temperature after the fifth injection. Seventeen days later, following another injection, an immediate and more severe generalized urticaria developed within a few minutes and lasted two to three days. In December, 1948, M. Gelfand[4] presented a case of mercuhydrin sensitivity in a man who developed chills and fever (103° F.), retrosternal distress and weakness after the fifth intramuscular injection of mercuhydrin which recurred ten days later following another injection.

We wish to add to the literature an unusual reaction of chills and high fever (105.8° F.) associated with a cutaneous eruption and exfoliative dermatitis of the palms of the hands in a woman who received eleven injections before chills and fever first occurred. She subsequently developed an accelerated reaction to injections begun fourteen days later. An immediate reaction ensued within one-half hour after the final injection thirty-two days later. Because of the unusual opportunity afforded us to observe this patient in these three stages of sensitization and because of the infrequent occurrence of such untoward reactions, we felt this case was worthy of report.

CASE REPORT

F. L., a forty-eight-year-old widowed Negress, was admitted to Sydenham Hospital on December 2, 1948, with a history of substernal oppression of two weeks' duration and subsequent dyspnea and orthopnea. Digitalis was taken for one week with little or no relief, and during the five days prior to admission she experienced increasing substernal pressure, hemoptysis, chills and slight fever. The past history was essentially negative. The personal and family history of allergy was also negative. Venereal disease was denied.

On admission the patient was acutely ill, moderately dyspneic with a temperature of 102° F. The pulse was 110 per minute, Corrigan in type; the blood pressure was 136/58. The lungs showed moist râles at the bases posteriorly; the heart was enlarged to the left, and loud systolic and diastolic murmurs were heard over the base transmitted down behind the sternum. A soft systolic and diastolic murmur was also heard at the apex. The liver was felt three to four fingers below the costal margin and was slightly tender. There was some pre-tibial and ankle edema. A diagnosis of congestive heart failure and luetic heart disease with a double aortic lesion

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was made. The patient was given digitalis leaf, 1:5 gr. (0.1 gm.) and ammonium chloride, 30 gr. (2.0 gm.) daily, and also, 2.0 c.c. of mercuhydrin intramuscularly. The condition remained practically unchanged in the first week. The temperature ranged between 101° F. and 99° F.; the moist râles were still present at the bases, and the dyspnea was only mildly relieved. The white blood cell count ranged from 5,100 to 12,500 with a relatively normal differential. The hemoglobin was 67 per cent; the sedimentation rate, 22 mm. The blood urea nitrogen was 19.6 mg. per cent and the total serum proteins, 7.5 mg. per cent. The blood serology was 4-plus with the Mazzini and Kline tests. The blood cultures were negative. The urine showed a trace of albumin and a few hyaline and granular casts and was negative on culture. X-ray of the chest showed marked enlargement of the heart to the right and left, also some evidence of pulmonary congestion.

Because of the low-grade fever and the apical murmurs, concurrent rheumatic heart disease was considered as well as subacute bacterial endocarditis. On the eleventh day after admission the patient experienced a shaking chill and fever, the temperature rising to 102.4°F. The following day she was afebrile. On the thirteenth day another chill and fever occurred, the temperature rising to 105° F. This repeated itself on the fourteenth, fifteenth and sixteenth days, with a temperature of 105.8° F. on the last day. The diagnosis of subacute bacterial endocarditis was more seriously considered but the blood cultures remained negative. At this time it was suggested[3] that the chills and spiking temperatures might be due to the mercuhydrin which the patient had been getting intramuscularly daily since admission. The mercurial diuretic was discontinued, and the chills and fever did not recur. From the sixteenth to the thirtieth day the temperature ranged from 99° F. to 100° F. The general condition improved and x-ray of the chest showed marked reduction in the size of the heart. On the twenty-sixth day after admission there developed a pruritus of the palms of the hands which eventually developed into an exfoliative dermatitis and lasted for two to three weeks. On the thirtieth day mercuhydrin therapy was resumed. The same dose, 2 c.c., was given intramuscularly with no untoward reaction. This was repeated on the thirty-first day with no side effect but on the thirty-second day chills and fever occurred, the temperature rising to 105.4° F. On the following day the temperature rose to 102° F. and mercuhydrin was again discontinued. Associated with the chills and fever were dull retrosternal pain and "numbness and burning sensations of the legs." Sensitivity to mercuhydrin was strongly suspected. About a week later there appeared a fine desquamation over the lower abdomen and back and upper thighs. From the thirty-third day after admission to the sixty-fifth day, no mercuhydrin was given and the temperature remained practically normal except for one rise to 102° F. On the sixty-fifth day a much smaller dose, 0.5 c.c., of mercuhydrin was given intramuscularly and close observation of the patient was ordered and carried out. Within one-half hour she experienced tingling sensations all over the body including the lips and tongue, and at the end of one hour she complained of generalized pain involving the upper and lower extremities, the back, and especially, the lumbar region. Soon after, severe headache developed, at first occipital and then frontal. One-half c.c. of epinephrine hydrochloride (1:1000) was given subcutaneously, and seconal, 1½ grains (0.1 gm.) by mouth. The temperature, pulse and respiration remained unchanged. The blood pressure was unaltered. The patient was watched constantly. She had a restless night and complained of headache and pains in the extremities. In early morning the temperature rose to 100.6° F. but returned to normal that day. No chills occurred. There was marked diuresis, 2200 c.c. of urine within six hours. Fatigue and weakness persisted for three days. Subsequent injections of saline and aminophylline, 1½ grains (0.1 gm.) intramuscularly caused no untoward reactions. She was discharged on the seventy-fifth day, much improved.

Skin tests performed with the scratch method with mercuhydrin, mercupurin and

salyrgan were totally negative. Intradermal tests were likewise negative. Patch tests with these substances were negative after forty-eight hours and again negative when read two days later. The scratch-patch test recommended by Gottlieb elicited traumatic irritation no different from control patients. Finally, the serum from a patient receiving mercuhydrin for seven consecutive days without untoward reactions was employed for intradermal testing in our patient with negative results. (Leftwich technique). All the above tests were repeated. No positive skin test could be demonstrated in this case to any of the mercurial diuretics with any method of skin testing.

DISCUSSION

There can be little doubt that the chills and fever present in this case were due to the injections of mercuhydrin. The time intervals for the development of these manifestations are of striking significance inasmuch as the symptoms first appeared on the eleventh day in the first course of treatment, on the third day of the second course and within one-half hour after the final injection given one month later. These reactions seem to correspond to the three phases observed in the classical induced form of hypersensitiveness, namely, serum disease, and include the initial, the accelerated and immediate reactions. Similar time intervals may occur in sensitization to other drugs, biologicals, chemical agents, antibiotics and other substances. Rarely, however, have all three phases been reported in patients with mercuhydrin sensitivity. In most instances the immediate reactions have occurred at the onset of the second course of treatment. We had the unusual opportunity of observing all three phases of acquired sensitivity in this case.

The most common allergic reactions from the mercurial diuretics are the cutaneous manifestations, such as urticaria, angioneurotic edema, exfoliative dermatitis and erythematous eruptions. While our patient developed an exfoliative dermatitis of the palms of the hands and a desquamation of the lower abdomen and upper thighs, nevertheless, these manifestations were not the predominant side effects.

Other reactions, such as chills and fever and anaphylactoid shock, are less commonly observed but are usually more serious in nature. They are frequently but not always preceded by cutaneous eruptions which should serve as a "danger signal" for further therapy with the mercurial diuretics. It is quite possible that some of the fatal reactions reported might have been avoided if this warning had been taken into account. Discontinuance of the drug is the safest procedure rather than the substitution of one preparation for another.

Skin tests with these drugs are most frequently negative. This is true of drug allergy in general, where symptoms of asthma, urticaria, angioneurotic edema, dermatitis, et cetera, occur from simple chemicals, such as aspirin and aminopyrine, in individuals with totally negative skin tests and with the absence of circulating antibodies. The explanation for clinical sensitivity to drugs in humans, and the failure to demonstrate positive skin reactions, is not fully understood. Most authorities are inclined to apply the

theory of Landsteiner from his work on sensitization in animals with simple nonprotein chemical substances. In a large series of experiments Landsteiner[6] and his co-workers were able to produce sensitization and anaphylaxis with a nonantigenic substance by combining it with a protein or large molecule. The new conjugated substance specifically sensitized animals and acted as a true antigen. The chemical was regarded as a hapten, and subsequent injections of this substance alone or in conjugated form could produce typical anaphylactic reactions. If this mechanism holds true for human drug allergy, it can explain clinical hypersensitivity to drugs, nonprotein in nature, in individuals with negative skin tests. Enough proof, however, has not yet been established to substantiate this theory.

In our case of mercuhydrin sensitivity, skin tests with the scratch, intradermal and patch methods were totally negative. The scratch-patch test was also negative. Three different mercurial diuretics were used. Burrows and Stokes,[1] however, reported positive patch tests in cases with erythematous eruptions due to the mercurial, neptal. Gottlieb reported a case of a man who developed generalized urticaria from mercupurin and showed positive scratch-patch tests to the drug. Gelfand's case of mercuhydrin sensitivity showed negative intradermal tests but a positive reaction to the Leftwich technique. This test was described by Leftwich[7] and employed by him as an aid in the diagnosis of hypersensitivity to the sulfonamides. Serum was obtained from individuals taking sulfonamides orally without untoward reactions and used for intradermal tests in patients who manifested drug fever from these agents. Positive reactions were obtained in twenty-eight out of thirty cases, or more than 90 per cent. It is believed that the drug combines with the plasma protein, *in vivo*, forming a complex sensitizing antigen capable of producing a positive skin test. In our case this technique was followed with serum obtained from two mercuhydrin-treated individuals for seven days, and negative results were obtained with both sera. Further studies along these lines with this technique are indicated.

It should be noted that toxic reactions also follow the use of mercurial diuretics. These symptoms are referable to the gastrointestinal, urinary, cardiac and central nervous systems. They are more commonly observed in patients with renal and wasting disease. Several sudden deaths have been reported[2] following the intravenous administration of these mercurials, and they were attributed to the toxic effect on the heart with the production of ventricular fibrillation. No fatalities occurred with the intramuscular or rectal route of administration.

SUMMARY

1. A case of mercuhydrin sensitivity with chills, high fever and an exfoliative dermatitis is recorded.

2. Skin tests with the scratch, intradermal, patch and scratch-patch methods were totally negative with mercuhydrin, mercupurin and salyrgan. The Leftwich technique was also negative.

3. Hypersensitivity to the mercurial diuretics, while rare, may be se-

rious in nature and should serve as a warning against further treatment with these drugs.

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COTTONSEED PROTEIN vs. COTTONSEED OIL SENSITIVITY

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ALLERGIC TOXEMIA AND FATIGUE

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ORAL PROCAINE HYDROCHLORIDE THERAPY IN ASTHMA

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STATUS ASTHMATICUS is defined by Piness as "an asthmatic condition that does not respond to the ordinary methods of treatment."[3] The May 29, 1948, issue of the *Journal of the American Medical Association* presents a panel discussion on the available methods of treatment of acute and chronic asthma. All forms of therapy are discussed, with the exception of two methods used almost routinely and with excellent results in the leading clinics abroad. These are the intravenous administration of procaine hydrochloride in normal saline solution and the blocking of the stellate ganglion, vagus nerve and cervical sympathetics with the same drug.[1] The Queries and Minor Notes of the August 21, 1948 issue of the same journal mentions the work of State and Wangensteen,[4] who used intravenous procaine in the treatment of urticaria and serum sickness with excellent results.

We have surveyed the available literature and cannot find any reference to the use of procaine hydrochloride orally in the treatment of this condition. Because of the dramatic and persistent relief which we obtained in one patient by this method, we feel justified in bringing it to the attention of the medical profession. This is entirely a preliminary report, without any effort being made to explain the result obtained, the pharmacology, physiology, or mechanics of the effect. We believe the action of the procaine may, in reality, be due to its breakdown products, diethenol-amine or para-aminobenzoic acid.

CASE REPORT

The patient, M. F., a white girl, was eighteen years old.

Past History.—Following an attack of pneumonia at the age of two, the patient's mother noticed an increasing respiratory distress which was finally diagnosed by the attending pediatrician as asthma. Various medications were instituted by different doctors over the next six-year period with only slight or temporary relief of the asthmatic condition. The attacks occurred spasmodically, with no seasonal incidence, and were of varying intensity, but were always preceded or complicated by an upper respiratory infection. During this interval, most relief was obtained by the use of epinephrine injections which were given almost every week.

In 1939, she was admitted to the Bobs Roberts Pediatric Division of the University of Chicago Clinics where a complete examination and study were made. Allergy skin tests undertaken at this time revealed sensitivity to feathers, eggs, chocolate, milk, house dust and dog hair. Epinephrine was given by injection and by mouth, but satisfactory results were noticed for only short intervals. After discharge from the hospital she was placed under the care of an allergist who administered autogenous

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vaccines three times a week. These were discontinued after several weeks when absolutely no relief was obtained and after she developed rather severe local and systemic reactions.

At the age of ten, she again had pneumonia which required four months' hospitalization. At the age of eleven, she was readmitted to the Bobs Roberts Hospital for further study, but no change was noticed in her skin reactions to another series of skin tests.

From this time to 1943, the patient stated that she had only a period of three months' duration in which she was completely free of attacks, and was able to attend school regularly. Since 1943, she has not been free of attacks for longer than forty-eight hours. From 1946 to December, 1947, she was under the constant care of an allergist who gave her specific immunizations, all the present available antihistamine drugs, and the newer antiasthmatic preparations available, with only slight relief at any time. After repeated use of several of the antihistaminic drugs, she developed rather violent drug reactions, manifested by headache, nausea, vomiting, nervousness, skin rashes, et cetera.

Present History.—On December 21, 1947, the patient was seen for the first time by one of us (M.M.S.) in an acute asthmatic attack that had been increasing in severity for over five hours and had not responded to any of the wide variety of available drugs in her stock. She was in extreme distress, leaning forwards in bed, grasping her legs, and gasping for air. Her respirations were so labored that they were audible almost fifteen feet away. The patient was rather deeply cyanotic, her eyes were widely dilated, the nares flared, and the whole chest heaved with every breath. The abdomen was forcibly retracted and every accessory muscle was utilized in breathing. A profuse perspiration was on the forehead and face, the pulse was bounding and could barely be counted. She had received a total of 1.5 cubic centimeters of epinephrine by injection before my arrival. She was given immediately one-quarter grain of morphine followed by a slow intravenous injection of seven and one-half grains of aminophylline. Within a half an hour, definite improvement could be noticed, with a slowing of the pulse, less labored breathing and a lessened nervousness. Another injection of morphine was given and within the hour she fell into a fitful sleep, with decided improvement of respiration.

Between December 21, 1947, and April, 1948, the patient was seen once or twice each week for almost identical attacks, which were not completely relieved by the intravenous administration of aminophylline. The medication varied considerably and included every new drug introduced on the market. As a rule partial relief was obtained from all, for periods lasting from three to seven days, but after this interval, no further relief was afforded by any of the marketed drugs, either alone or in combination. Most were given in maximum doses. During this time, the patient was totally unable to work, was almost always in bed, with the least effort bringing on a severe attack. She lost the appetite that remained, and was deteriorating rapidly both mentally and physically.

It was during this time that the case was brought to the attention of the co-author (M. S.) who suggested the possibility of either an intravenous procaine injection or a stellate ganglion block. Reference was made to the work of Donoso,[2] who described the mechanism of asthmatic reactions and the etiology of bronchial spasm, demonstrating that novocaine could relieve the constriction and restore the lumen of the bronchi and bronchioles through its antihistamine action. The matter was discussed thoroughly, and we felt that because of the apparent hopelessness of the case, any effort to break the severe bronchial spasm present here should be attempted. The seriousness of the situation was then discussed with the patient and her family, emphasizing the purely experimental aspects of the therapy, the little

there was to offer, and promising little hope of recovery. The patient was admitted to the American Hospital, April 12, 1948.

Hospital Course.—Physical examination on hospitalization revealed that the heart tones were irregular, definitely stronger on expiration, becoming barely perceptible on inspiration. There was a moderate pulsus paradoxus. Anterior cardiac diameter was enlarged to the right. The lungs revealed numerous sibilant, sonorous and subcrepitant râles over both lung fields, continuous during inspiration and expiration. Laboratory examination was not contributory. X-ray of the chest revealed a generalized pulmonary emphysema, with nodular infiltrations of both apices. Reexamination of the lungs on April 22, 1948, revealed no evidence of an active pulmonary pathologic condition, but no decrease in the emphysema.

One hour after hospitalization, skin sensitivity tests with procaine hydrochloride, 1:1,000 and 1:100 dilutions, using normal saline as control, were performed using the flexor surfaces of both arms. There was almost immediate severe reactions to both dilutions, with a wide area of erythema, a large urticarial wheal with pseudopods and intense itching. A delayed generalized reaction to the skin tests was noted later that same evening when the patient developed a severe asthmatic attack lasting until the next morning. Intranasal oxygen was given, but discontinued since it apparently made her feel worse. The day after the skin test, the patient was so nervous that she required five injections of Demerol (100 mg. each) and was given Trasentine by mouth.

In spite of the skin sensitivity to the procaine solution, it was decided to give her a small intravenous test dose, using a 1:100,000 dilution in distilled water. After eight minutes running time the patient developed an alarming reaction, with a sudden respiratory arrest, intense dyspnea, marked flushing of the face and extreme nervousness. One hundred milligrams of Demerol gave absolutely no relief. The patient would not tolerate pure oxygen by mask. As a last resort 7.5 grains of aminophylline were given intravenously very slowly, with much relief in a short time. One hour after the injection, the patient vomited but seemed to rest comfortably for three and one-half hours.

The entire hospital course was very stormy, requiring an almost constant vigil by one of us or by one of the resident hospital staff. Following the second intravenous injection of aminophylline, the patient developed a shock-like syndrome, with barely perceptible pulse, shallow respirations, unrecordable blood pressure, et cetera. The attending intern remained on constant call and eventually, by using various drugs, brought about recovery. During the stay in the hospital, she was given a course of deep x-ray therapy to both lungs as recommended by some for this condition, but with little relief.

She was discharged thirteen days after admission in fair physical condition, with definitely improved mental state, better appetite, but rather discouraged by failure to perform the proposed block.

Post-Discharge Course.—Because of a sudden pain in the right lower quadrant associated with nausea and vomiting she was readmitted to the hospital on May 19, 1948. Several years previously, she had been told that she had a subacute appendix, but because of her asthmatic condition, the previous physician would not operate. On admission, her pain was localized over McBurney's point, with point tenderness, referred pain, and rebound tenderness. Blood count was slightly depressed, but because of her associated condition, little regard was placed on it. She was put to bed with an ice bag to the right lower quadrant, given no medication, and given nothing by mouth. As her pain did not subside, but gradually increased in severity, with more nausea and vomiting, and a slight increase in the blood count, it was felt safer to interfere in spite of her asthmatic condition.

Under cyclopropane-pentothal anesthesia (given by M. S.) an appendectomy was performed on May 21. The appendectomy was accomplished with very little difficulty or complications. The anesthetic was very well tolerated and rather readily administered. Except for one very slight asthmatic attack on the first postoperative day, the patient did not have a further single episode. She was ambulatory on the third postoperative day and was discharged from the hospital on the seventh postoperative day.

This complete disappearance of asthmatic manifestations was rather a surprise to us, and we were at a loss to explain the mechanism, but our optimism was not for long, because within one week after discharge, we were advised of a slight attack. As the summer started, the attacks gradually increased in severity, were closer together, but did not become as severe as before the operation. We felt that since prior experience showed poor response to all accepted therapy, and that since it was impossible to resort to either procaine intravenously or a stellate block, something drastic had to be done for this patient to prevent a recurrence of her previous condition. By this time, she had started to gain weight, was eating better than at any time previously, was active and mentally happy. Nothing that we could find in the literature was of any help, so again, after discussing the problem among ourselves, we decided to attempt the use of procaine hydrochloride by mouth. This was purely an experimental measure, since we did not know the correct dosage, the toxic effects on the patient, or the effect on the asthmatic attacks. It was with some hesitation that we prescribed our first oral doses.

On July 15, 1948, the drug was started in doses of 10 grains four times a day, even while the patient did not have an attack. She was seen weekly and observed for toxic manifestations. During this time, she had two slight attacks of asthma which were not relieved by the drug. After ten days the dosage was increased to 12.5 grains four times a day. Later, when it was learned that most of the attacks occurred on arising in the morning, and slightly before retiring, the dosage schedule was changed so that 25 grains were taken before she arose in the morning and 12.5 grains were taken before retiring.

Within three days of this schedule, the patient noticed that there was absolutely no tightness in the chest on arising in the morning and that her breathing during the day was easier. She has had absolutely no attacks of asthma since July 31, 1948. Her appetite has improved 100 per cent, she has gained 35 pounds, has returned to work and does not look like the same patient who entered the hospital. She cannot believe that she has had five months without a single attack. In order to test the effect of the drug, it has been withdrawn on three occasions for a period of seventy-two hours, with an immediate return of respiratory distress, tightness in the chest, and a definite asthmatic attack. This can be aborted by immediately giving the drug by mouth.

We have noted absolutely no side reactions, the blood count remains normal, the lung fields show pulmonary emphysema but no active pulmonary pathology, and the appearance of the patient, her mental and physical well being, attest for the efficiency of the drug.

SUMMARY

A case of intractable asthma has been presented which did not respond to any of the accepted remedies available today. An attempt to abort the asthmatic state by the use of procaine intravenously and by stellate block was impossible because of the patient's sensitivity to the drug. As a last resort, and by a method of therapy not heretofore reported in the literature, the patient was given procaine hydrochloride by mouth with dramatic and

persistent relief. No explanation is offered as to the mechanism of action of the drug so administered.

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ADDENDUM

When last seen by one of us (M.M.S.) in September 1949, the patient was in excellent health, having only minor abortive asthmatic attacks, usually occurring when she dropped the maintenance dose of procaine hydrochloride by mouth. From the inception of treatment July 15, 1948 to the date last seen, the patient had taken approximately 15,000 grains of procaine without any side effects, abnormal changes in the blood or body fluids, or without demonstrating any abnormality that could be detected by any laboratory means available at the present time.

COTTONSEED PROTEIN VS. COTTONSEED OIL SENSITIVITY

(Continued from Page 25)

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ENTERIC-COATED ANTIHISTAMINICS

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THE PRESENT series of studies was started before any enteric-coated antihistaminic drugs were generally available. The purpose of this work was not to prevent the absorption of the drug for a period of time but rather to see what effect slower absorption would have on the amount of relief from symptoms, the continuity of relief and the development of side reactions.

It has been frequently noted that as the amount of antihistaminic drug taken per given period of time has been raised, so also were the percentage of patients experiencing side reactions from the drug. Therefore, if less of the drug could be given and symptoms adequately controlled, fewer side reactions might be expected. Certain of the side reactions are undoubtedly due to local irritant action on the gastric mucosa and others to the amount of the drug actually circulating in the blood. By enteric-coating the tablets, no medication comes in contact with the gastric mucosa, and if the amount of drug ingested can be reduced, certainly there would be less in the circulating blood.

Neo-Antergan (Merck), N-p-methoxybenzyl-N', N'-dimethyl-N-a-pyridylethylene diamine maleate,[3-8] was selected since side effects have been encountered in approximately 25 per cent of patients receiving it[1] and it was felt that if enteric coating is of value, it should be effectively demonstrated with this preparation. As Feinberg[2] stated that, in his experience, Neo-Antergan was of benefit in thirty-nine of sixty patients with hay fever and eight of ten with perennial rhinitis, patients presenting these two conditions were used in this study.

The enteric coating used was composed entirely of cellulose acetate hydrogen phthalate. The coating on regular Neo-Antergan tablets is a conventional sugar-coating. Cellulose acetate hydrogen phthalate differs from other enteric coatings, which are insoluble in acid and soluble in alkali, in that it is dissolved by the action of the enzymes of the small intestine. Tablets coated with cellulose acetate hydrogen phthalate may begin to disintegrate as soon as they reach the small intestine. Delayed-action Pyribenzamine tablets are not coated with cellulose acetate hydrogen phthalate, and their action does not begin until four or five hours after ingestion.

While comparison between enteric-coated and plain Neo-Antergan might have given sufficient data, it was decided to also give each patient one of the other antihistaminics in order that the studies might be even better controlled. These drugs, of course, were not enteric coated.

A complete treatment and questionnaire sheet was kept on each patient.

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TABLE I. TREATMENT PATIENTS RECEIVED OTHER THAN ANTIHISTAMINES

	No. Patients	Hyposensitization		No Treatment
		Preseasonal Treatment	Coseasonal Treatment	
Hay fever	19	8	6	5
Hyperesthetic rhinitis	12	5		7

TABLE II. ENTERIC-COATED NEO-ANTERGAN VS. PLAIN

	No. Patients b.i.d.	No. Patients t.i.d.	No. Patients q.i.d.	Improved	Not Improved	Side Reactions
Enteric coated	31	7	2	29 (96%)	2 (4%)	0
Plain		26	5	27 (87%)	4 (13%)	4 (13%)

The information obtained on each of the semi-weekly visits as well as the medication prescribed and its frequency were noted thereon. Those also receiving injections had each specific treatment recorded on a standard form.

Thirty-one patients, nineteen with hay fever and twelve with hyperesthetic rhinitis, were selected. The drugs were not used in the same order more than could be helped, some patients being started on plain Neo-Antergan, others on enteric-coated Neo-Antergan, and others on the various antihistaminics used.

Patients were continued on one drug for a minimum of five days, ragweed hay fever victims being treated from about August 20 to September 10—there being little change in the ragweed pollen count during this period. Of the nineteen patients with hay fever, eight received preseasonal treatment, six coseasonal treatment and five no pollen treatment. Of the twelve patients with hyperesthetic rhinitis, five received hyposensitization injections and seven none (Table I). As far as could be determined, no changes were made in environmental exposures over the period of the experiment.

Improvement, in general, meant greatly lessened sneezing, nasal discharge and nasal blockage. With enteric-coated Neo-Antergan, twenty-nine were improved, of whom two with hyperesthetic rhinitis noted only less nasal blockage. One with hay fever and one with hyperesthetic rhinitis noted no improvement. With the plain Neo-Antergan twenty-seven were improved. Of those unimproved, the same two who noted no improvement with the enteric-coated tablets noted none with the plain, and the same patients with hyperesthetic rhinitis noted only improvement in nasal blockage.

Enteric-coated Neo-Antergan was given to all patients twice daily, to seven, three times daily, and to two, four times daily. In six of the seven, no additional benefit was found on increasing the dose, while one patient (with hyperesthetic rhinitis) felt that more of the drug gave added improvement.

Uncoated Neo-Antergan was not satisfactory for continued relief when given twice daily. Twenty-six patients were given three tablets daily, and

TABLE III. EFFECT OF OTHER UNCOATED ANTIHISTAMINICS ON SYMPTOMS

	Histadyl 50 mg.	Benadryl 50 mg.	Thephorin 25 mg.	Thenylene 100 mg.	Pyribenzamine 50 mg.	Diatrin 50 mg.	Decapryn 25 mg.	Totals
No. patients taking medication t.i.d.	1	7	4	7	8	2	2	30
No. patients taking medication q.i.d.	0	2	1	0	1	0	2	6
Total patients taking medication	1	9	5	7	9	2	4	36
Improvement	1	9	4	4	9	2	4	32 (89%)
No improvement	0	0	1	3	0	0	0	4 (11%)
Side reactions	1	3	1	1	3	0	1	10 (28%)

TABLE IV.

ANALYSIS OF PATIENTS REACTIONS TO UNCOATED ANTIHISTAMINICS

	Hay Fever	Hyperesthetic Rhinitis	Total
Improved	20 (95%)	12 (80%)	32 (89%)
Not improved	1 (5%)	3 (20%)	4 (11%)

five received four. If dosage was carried higher, the side reactions overshadowed the additional relief.

On these dosages there were no side reactions from the use of enteric-coated tablets, while four patients (13 per cent) experienced side reactions from the uncoated tablets (Table II).

Twenty-six patients (84 per cent) preferred two enteric-coated tablets daily to three or four uncoated tablets for the following reasons: ten felt their symptoms were better controlled, fourteen received the same amount of relief with less medication, and two had side reactions from uncoated Neo-Antergan but none from the enteric-coated (Table VI).

Seven other antihistaminics were given, some patients receiving as many as three besides Neo-Antergan and others only one. None of these drugs adequately controlled symptoms when taken twice daily. In computing the results, the medication was taken three times daily by thirty patients and four times daily by six. These were the optimum dosages for the particular drug and for the particular patient. Again, an increase in the amount daily over four tablets led to a great increase in side reactions which overshadowed the additional relief.

The following antihistaminic agents were used: Histadyl (Lilly) 50 mg., one patient; Benadryl (Parke-Davis) 50 mg., nine patients; Thephorin (Hoffmann-LaRoche) 25 mg., five patients; Thenylene (Abbott) 100 mg., seven patients; Pyribenzamine (Ciba) 50 mg., nine patients; Diatrin (Warner) 50 mg., two patients; and Decapryn (Merrell) 25 mg., four patients. With this small series no additional information would be gleaned by analyzing each drug separately, so only the over-all results are given for comparison (Table III). Thirty-two (89 per cent) were improved; of these, twenty (95 per cent) hay fever patients were benefited, while twelve (80 per cent) of the hyperesthetic rhinitis patients received some relief. Of the four (11 per cent) who were unimproved, one had hay fever and the other three hyperesthetic rhinitis (Table IV). Side reactions occurred ten times (28 per cent), Benadryl and Pyribenzamine each provoking this effect on three occasions and the others once each.

TABLE V. PATIENTS PREFERENCE IN ANTIHISTAMINICS TRIED

	Preferred Neo-Antergan (ent.) to Plain	Preferred Neo-Antergan (ent.) to other Antihistaminics
Neo-Antergan (ent.) ..	26 (84%)	20 (65%)
Neo-Antergan (plain) .	3 (9%)	
Other antihistaminc ..		8 (26%)
No difference	2 (7%)	3 (9%)

TABLE VI. REASON FOR PREFERENCE IN ANTIHISTAMINICS

	Same Result with Less Medication	Better Control	No Side Reactions
Neo-Antergan (ent.) vs. Plain	14	10	2
Neo-Antergan (ent.) vs. other antihistaminics	5	12	3

Comparing enteric-coated Neo-Antergan with the other antihistaminics, twenty (65 per cent) preferred the former, eight (26 per cent) preferred the latter, and three felt that there was no difference (Table V). Of those preferring enteric-coated Neo-Antergan, twelve had better control of their symptoms with it, five obtained the same result with less medication, and three had side reactions with the other antihistaminics but none with enteric-coated Neo-Antergan while obtaining about the same relief with either (Table VI).

In comparing enteric-coated Neo-Antergan with uncoated other antihistaminics, one must take into account the fact that if both were either coated or uncoated, there are many who might prefer some other antihistaminic to Neo-Antergan. This makes the figure of 65 per cent who preferred enteric-coated Neo-Antergan to the other uncoated antihistaminics tried all the more remarkable.

DISCUSSION

On analyzing these results it would seem that an enteric-coated antihistaminic gives as good results generally as the uncoated with certain advantages and disadvantages. Advantages: taken less often, smaller dosage, and fewer side reactions. The effectiveness of the drug rises to a certain level and remains there during the day and the night. Disadvantage: reduced speed of action. The uncoated antihistaminic acts faster—generally in twenty minutes, while the enteric-coated tablet taken on an empty stomach takes about thirty minutes—but with the uncoated the relief lasts only up to three or four hours before the symptoms return. The graph of relief would be one of waves unless additional medication were taken before the effects of the preceding medication had worn off. The enteric-coated graph of relief would rise more slowly but would be maintained as a straight line, gradually declining after six to twelve hours.

No attempt was made to estimate the amount of relief in the patients studied since this is entirely subjective and the excellent results obtained in one patient would be considered as only fair in another. For this reason, no analysis was made on the kinds of hyposensitization given. It is well known that the antihistaminics give more relief in the hyposensitized patient and such was our experience, but again returning to the graph of relief of

symptoms, such a patient is starting at a higher level (some relief) and therefore would naturally be expected to obtain a higher percentage of relief than a patient who had had no treatment.

In discussing relief, only three symptoms were emphasized because all the patients in the series had these symptoms. Not all were relieved in all patients—even though results were excellent—nor was there any definite pattern, some experiencing more relief of one symptom, such as nasal blockage or discharge, and others, relief of all nasal, eye and mouth symptoms.

While in this series no combination of enteric-coated and uncoated antihistaminics was tried, such might be of benefit in selected cases. In our experience, the time of absorption of enteric-coated tablets is but little longer than the uncoated and therefore it scarcely seems advisable to give both at bedtime on an empty stomach. While the coated tablet will act through the night, the additional amounts of the drug in the uncoated tablet might cause side reactions or insomnia.

SUMMARY

Enteric-coated tablets of Neo-Antergan, while not acting as quickly as the uncoated, appear to achieve a smoother and longer-continued action and will give as good relief from the symptoms of hay fever and hyperesthetic rhinitis, in most cases, with fewer side reactions and in less quantity, than do uncoated tablets.

It is not maintained that two enteric-coated tablets per day is the best dosage of Neo-Antergan or any other antihistaminic. This can only be determined in each individual case with the preparation being used. In our series, two patients felt they had better relief on three tablets a day than two, although they preferred two of the enteric-coated tablets to four a day of plain Neo-Antergan.

Note: The author wishes to acknowledge with thanks the assistance of Dr. R. C. Pogge of Merck & Co., Inc. in making available supplies of Neo-Antergan tablets, enteric-coated and plain.

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BEHAVIOR OF THE NORMAL HISTAMINE OF THE RABBIT TOWARD ANTIHISTAMINIC SUBSTANCES

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NOTWITHSTANDING all that has been published on antihistaminic agents, little is known of their course of action. From the works of Staub we know only that the antihistaminic substances 929 F and 2339 R.P. (Antergan) neither activate, combine with, nor destroy the histamine.

In order to support the latter two points of view, namely, that antihistaminic agents neither destroy nor combine with histamine, we have carried out the following experiments.

METHODS

A group of twelve rabbits, chosen only because of the considerable content of histamine in their blood, were subjected to a determination of histamine before being injected with the antihistaminic agent; blood was then extracted by intracardiac puncture, and, in some cases, by bleeding.

The blood was collected with a syringe or a heparinized vessel. The antihistaminic chosen was Antistine* (2-N-phenyl-N-benzyl-amino-methyl-imidazoline) and, in two cases, Benadryl (beta-dimethyl amino-ethyl-benzidryl-ether hydrochloride).

These substances were administered to the animals intraperitoneally and in quantities always greater than those marked as sufficient and efficacious in preventing lethal anaphylactic shock.[6,9]

The determination of histamine was made according to the technique of Code, Marsoum, and Gaddum.

The results are shown in Table I.

DISCUSSION

Halpern mentions three different possible effects of the antihistaminics.

1. Diminution in the formation of histamine.
2. Acceleration in its destruction.
3. The lack of action on the receiving cells.

Other possibilities of the mechanism of action, such as the activation of the histaminase and its destruction and neutralization, have already been discarded (Staub, Chambon and Martin).

By utilizing Antistine, Staub has shown also that keeping this antihistaminic drug in contact *in vitro* with histamine for some time did not prevent activity. Later, the same author,[9] proceeding on the fact demonstrated by himself[3] that the injection of epinephrine increases the content of histamine, investigated whether this formative stimulus of epinephrine to produce histamine was neutralized or modified by the antihistaminics.

From the Section of Human Physiology of the Spanish Institute of Physiology and Biochemistry of the Superior Council of Scientific Investigations.

*Kindly supplied by CIBA, Commercial and Pharmaceutical Co., S.A., Barcelona.

TABLE I. BLOOD HISTAMINE BEFORE AND AFTER ANTIHISTAMINIC AGENT

No.	Antihistaminic Quantity in Mg. per Kg. Animal Weight	Histamine in Blood per C.c.		Antihistaminic Administered
		Before	After	
1	20	0.5	0.5	Antistine
2	25	0.002	0.002	Antistine
3	30	1.25	1.25	Antistine
4	60(30-30)	1.1	1.0	Benadryl
5	60	0.96	0.6	Benadryl
6	45	1.1	1.1	Antistine
7	40	2	2	Antistine
8	45	2	2	Antistine
9	60	2	2	Antistine
10	195(75-60-60)	1.5	0.075	Antistine
11	100	1.5	1.5	Antistine
12	90	1.1	0.66	Antistine

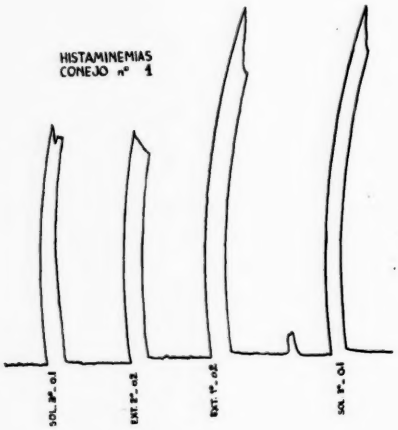

Fig. 1

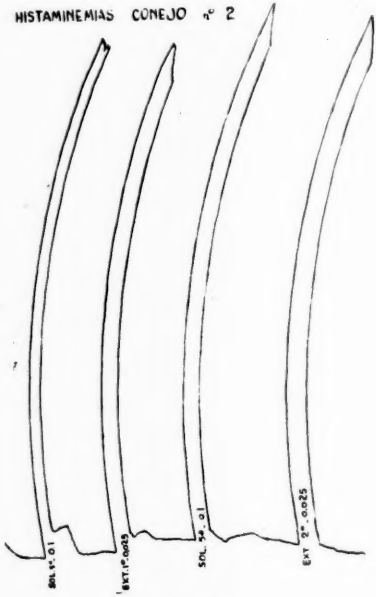

Fig. 2

His investigations confirmed the supposition that Antistine definitely acts by diminishing or annulling the hyperhistaminemia produced by the epinephrine. He concludes that the mechanism of action of antihistaminics consists in their restricting the formation or liberation of histamine.

If the mechanism of the action of the antihistaminics is not due to any inhibition of their formation, but to a displacement site of action, Staub would have found a greater quantity of histamine following injection of epinephrine, without giving rise to any abnormal phenomenon, since introduction of antihistamine would have protected the receiving cell from its toxic action. However, Staub finds that antihistaminics do act as brakes

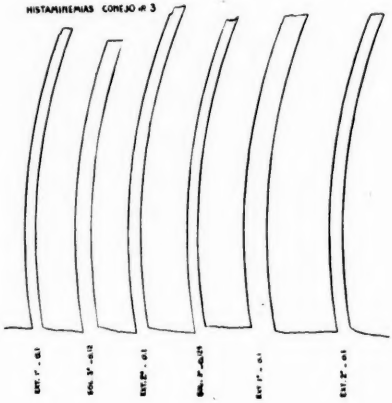

Fig. 3

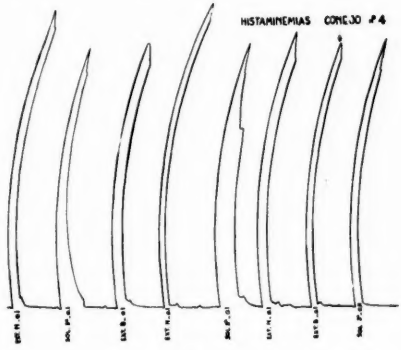

Fig. 4

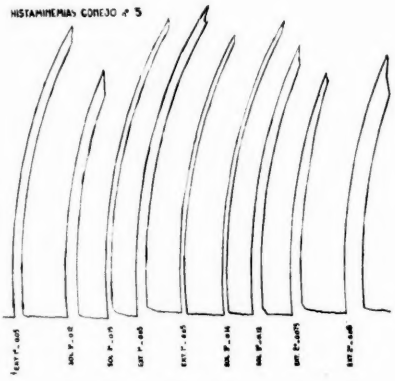

Fig. 5

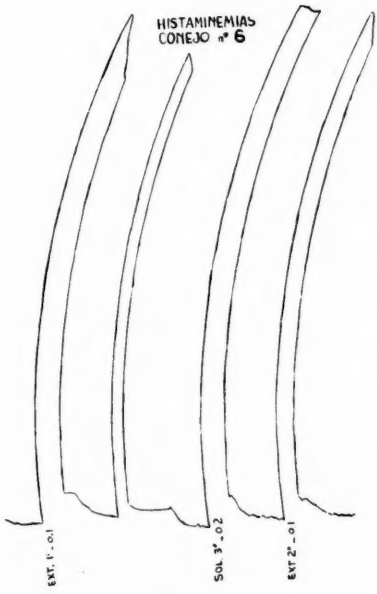

Fig. 6

upon the hyperhistaminemic mechanism of epinephrine, and, therefore, he maintains that the way in which these drugs act is simply that of restricting the formation of histamine.

It is generally accepted that the mechanism of action is that the antihistaminics displace the histamine from its point of attack (Halpern). Ackermann thinks the same of arginine and like substances. Roche and Silva have the same view for histamine derivatives.

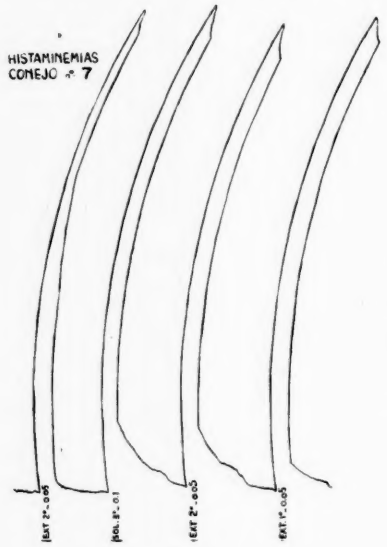

Fig. 7

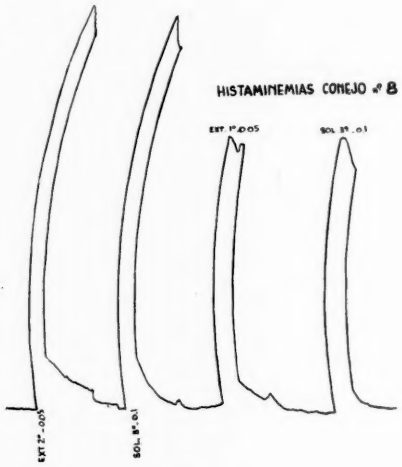

Fig. 8

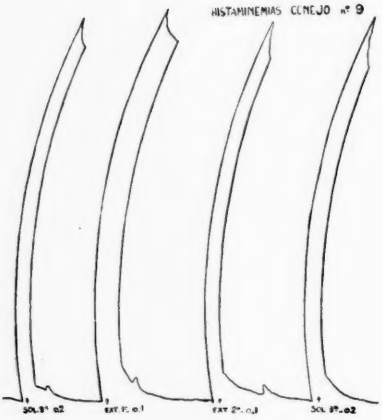

Fig. 9

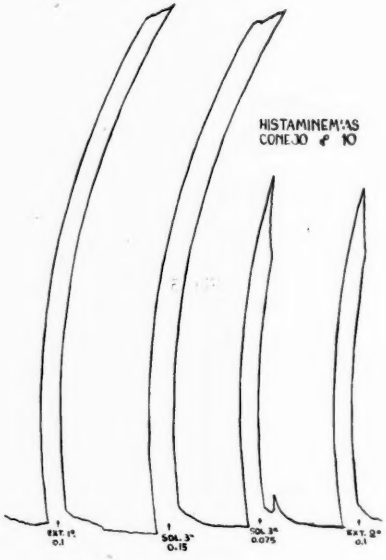

Fig. 10

Staub is of this opinion, for the 1571 F.H.; Halpern, for 2339 R.P. or Antergan; Mayer, for "Pyribenzamine"; Wells and Morris, for the benzo-hydryl-ethers; and Lehmann and Young, for anthracene-esters.

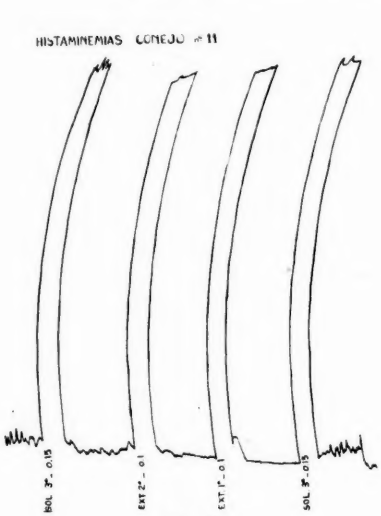

Fig. 11

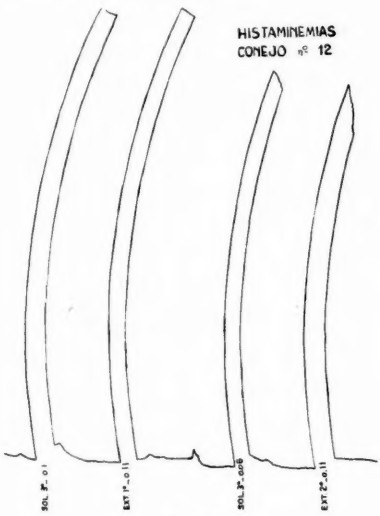

Fig. 12

We shall not discuss this as it is mentioned only as information and as our work is concerned with normal contents of histamine, where latter is already formed and of which there is no hyperformation.

Thus it may be concluded, as other authors have shown for other antihistaminics, that those used by us also do not destroy or neutralize histamine.

SUMMARY

1. Histamine determinations have been made on twelve rabbits before and after they received heavy doses of antihistaminics.

2. With the exception of four animals, the histamine level remained invariable in all, in spite of the fact that the majority presented evident symptoms of intoxication (paresis of the lower extremities, convulsions et cetera), and some of the animals died.

3. The resistance of the physiological histamine in the presence of antihistaminics leads us to believe that the mechanism of action of these drugs is distinct from that of neutralization or destruction.

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EMOTIONAL TRAUMATA PRECEDING THE ONSET OF ALLERGIC SYMPTOMS IN A GROUP OF CHILDREN

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IT HAS LONG been remarked by allergists and others that certain events in their patients' lives have seemed to precipitate the onset of clinical symptoms. The onset of symptoms after physical illnesses such as pneumonia, or after operations such as adeno-tonsillectomy, has been frequently noted. More recently attention has been turned to emotional as well as physical episodes.[1,2,3,4] As a matter of fact, the question has been raised whether the so-called precipitating physical causes, such as pneumonia or adeno-tonsillectomy, may not also have carried with them an emotional etiological component.

The present paper deals with a sample of ninety allergic children with ages ranging from one year and eleven months to eighteen years (mean: 8.8). The subjects were studied both medically and psychologically. This involved the usual medical history, physical examination, skin testing and such other laboratory procedures as seemed indicated. In addition, psychological interviews were held in each case with the mother and frequently with the father. Either a diagnostic play session or an interview was held alone with the child, depending on the age.[5]

In obtaining information from parents and older children, incidents in the life of each patient preceding the first onset of allergic symptoms were investigated. The procedure was not that of immediately firing a whole series of questions. It consisted, rather, of stating that anything that had bothered the patient or his parents might be of importance, and then, as John Mitchell, for instance, has done,[8] taking a listening and acceptant role. By this method not only was much factual information obtained, but very often, either consciously or inadvertently, episodes were related to the first onset of symptoms which had not been previously connected with it. Questions could then be used to fill in the gaps.

The traumatic episodes came to light usually in the interviews with the parents.

For example, the mother of a six-year-old asthmatic girl, at the beginning of her session with the psychologist, said that the doctor had thought the child's illness might be partly due to emotions, but she could see nothing of that sort. Sandra was a good child and well adjusted. "She never seems to get upset." She then said, apologetically, "I'm the nervous one." The psychologist reflected, "You feel your nervousness means something."

"Yes," nodded the mother. "I've been terribly upset." She went on recounting her own difficulties with the child's father. "It makes me so nervous, I don't ever feel he likes me. Once, Sandra said she didn't like me either and I got so upset.

Presented at the Fifth Annual Meeting of the American College of Allergists, April 14-17, 1949, Chicago, Illinois.

She was three. I remember it clearly because that was one time she did get upset. I was very hurt and cried and said I'd go away and she could get another mother. I couldn't stand talk like that. She sobbed and sobbed, not like just regular crying. She was terribly upset. I couldn't comfort her. She sobbed for hours and hours. I couldn't get her to stop. She was sick that night . . . " The mother paused, "I guess that was when the asthma started. Come to think of it, she'd never had it before."

Sometimes the traumatic episode was brought to light in the interview with the child.

Thus, an eighteen-year-old asthmatic girl who had been referred for severe and intractible eczema which had appeared for the first time in her life two weeks previously, at first declared that she could see "nothing special" to have made her break out. However, as she talked to a sympathetic listener whom she soon found did not condemn her, she brought out material that made the traumatic incident preceding the onset become clear.

Right before Christmas vacation she had been caught one night returning to boarding school with liquor on her breath. "They raised the most awful stink but *I* didn't think it was so bad."

"You're not quite sure but you're sort of proud of it," the psychologist reflected.

"But I was afraid they'd write my mother. I didn't know if they had or not and I didn't want to ask. I thought about it, though, all the way home on the train. At the station, my brother met me. He acted very mysterious. Mother was sick. I got scared.

"When I got to the house, she was in bed, all pale. She looked like death. I thought she was going to die. Then she told me she had cancer. I'd given it to her by being so bad. I didn't know whether to believe it or not; she'd always told me I'd be the death of her, when I wouldn't practice or any little thing. But anyway I felt like I was going to die . . . I couldn't sleep. I tossed and turned and began to itch. The next day I looked like sin; just as bad as I felt . . . "

With the younger children, sometimes the traumatic events came to light in the diagnostic play session and could later be confirmed by interview with the parents.

For instance, Richard, seven years old, who had had hay fever since infancy, was referred by a psychiatrist on two scores. He had been wheezing for a couple of weeks and had recently been caught choking his thirteen-months-old sister on the sly.

In his play session with a group of dolls representing his own family, he acted out a scene where he choked his baby sister. During this he said, "That's a bad thing to do. It doesn't mean he's loving her. She kicks and throws her hand over his mouth. She kicks him hard. Father and mother spank the boy and kiss the baby . . . The father says, 'Do you know how that felt?' And he starts to do the same thing to the boy. Only he choked him harder because he was bigger. Real, real hard. He fell down on the floor . . . Father said, 'I'm glad, that's taught that boy a lesson.' "

The father, at the mother's instigation, had actually choked the boy whenever he was caught choking the baby. Finally, in one of these episodes the child fell to the floor, seemingly unconscious, and the parents, overcome by guilt, stopped punishing him in this way. It was shortly after this that his wheezing began.

In his play, Richard went on to show what had happened after his father stopped choking him. Only now, the scene depicted what had occurred not in reality but in his own imagination, which to him, however, was almost as real.

"Then, everything got w-w-worse," he stammered and, then and there he started to wheeze. "Then," he went on, "they really *had* to get rid of him. They sent him out under a cobweb,—a big chokey came and chewed him up. Under the cobweb—all black—and he choked. They got all in his mouth . . ."

And a few minutes later he said eagerly, "He'd rather have daddy show him how it felt . . . Better than to throw him out and have him die."

Thus when his father stopped punishing him, Richard had taken over his own punishment. His wheezing was part of this.

From sessions such as these with both the parents and children, information on traumatic episodes apparently related to the first onset of symptoms were obtained in sixty-eight children. Separate traumatic events apparently related to the onset of separate syndromes were obtained in nine instances. Thus, although only sixty-eight individuals were represented, seventy-seven traumatic occurrences were noted preceding an initial onset for a given condition.

The largest number of traumatic episodes were seen to be related to the *loss or threatened loss of a parent.* This included the death of a parent, actual separation or desertion or what seemed to the child to threaten death, separation or desertion. In twenty-two cases episodes preceding onset of a particular symptom fell into this classification.

One child's asthma appeared at the age of seven after both her parents had been simultaneously killed in an accident. Three children (at the ages of three, five and eighteen, respectively) had come upon a parent drunk and had feared the parent actually dead. In his interview twelve years later, one of these recalled with evident emotion that he had found his mother fallen against the bathtub with blood running out of a gash on her head. "I thought she'd killed herself," he said. His father's reports confirmed the event and helped to ascribe the asthmatic onset to this date.

In five instances the mother left the child to go to work. In one instance the mother suddenly, and without preparation, turned over the entire care of the child to someone else. In six cases the mother's going away—to the hospital, on vacation or on visits without adequate preparation—preceded the first exacerbation, and in Sandra's case, already cited, the mother's threat of leaving was the antecedent event.

The threat of losing a parent may produce an emotional trauma in a child at an extremely early age. This is strikingly brought out in the case of a boy who, when seen at the age of five, was covered from head to foot with severe eczema. His mother related that the eczema began at eight months when she had left him to visit her husband who was then in the service in a distant city. That the event had made a deep impression was evidenced by the fact that the infant for months afterward would cry inconsolably whenever he saw a suitcase. At five years, the mother left the child again to go to work. At this time he had his first asthma attack.

There were three cases followed by onset where the parents left a child abruptly in school or hospital without preparation or where they told him

that they would send him away to school. Similarly, onset of symptoms followed (in two cases) when a child was locked alone in a room for an extended period, unheeded, and crying for his mother in vain.

From the records it appeared that to these children such occurrences stood as a kind of desertion. They felt that their mother had left them and often in their minds attributed this, bleakly, to having been somehow themselves to blame.

Death in the family, other than that of a parent, preceded onset in three cases.

However, the second largest class of incidents preceding the onset of allergic symptoms had to do with marital conflict. This does not refer to the long-term continuous conflict but to sudden eruptive episodes.

In one case, for instance, such an eruptive episode in marital conflict preceded the onset when a five-year-old girl saw her drunken father beat and threaten to kill her mother. It is interesting to note that still at eleven, her attacks recurred whenever the divorced father appeared on the scene.

In ten instances the emotional upset of the mother at the sudden discovery of the father's infidelity was followed by the appearance of clinical symptoms in the child. In two cases, the father's return from the service precipitated emotional upsets in the mother by the unwelcome resumption of marital relations, and in a third, by the necessity of giving up an affair. Family peace was disrupted (also in two cases) by sudden trouble in the father's business. In another case the child heard the mother's vituperative, screaming attack on the father, charging him with not caring about his children enough to support them. In another case the onset of symptoms followed the mother's decision to get a divorce; in another they followed the mother's foreswearing sexual contact on religious grounds; in still another they followed the civil war between father and mother which arose when the grandparents moved into their home.

With four children, the witnessing of intercourse preceded the onset of the first allergic symptoms.

To give an example, David, four years old, shortly after being moved into his parents' bedroom began screaming in his first attack of asthma. "The wolf," he cried, "the wolf is going to get me." In his play session he put the dolls representing the father and mother in bed together and the little boy doll representing himself in a bed close by. Then he placed the father on top of the mother and started to sob. "Had bad dream! Big bad wolf!" The therapist reflected, "The big, bad wolf scared him." "Yes," he nodded, and pointing to the father doll, he said, "There he is. Right there!" . . . David then took a toy gun and saying that he was shooting the big, bad wolf, he had the boy doll shoot the father. He then said, "I'm a naughty, naughty boy!" and shot himself.

Still another child, a boy, eight, recounted, "I wasn't too afraid; I was afraid though. They were bumping in the air, kind of. They were rumbling around. My dad was snorting, kind of. He looked like two big eyes—a devil. I guess I was real scared!"

To cite another example, Larry, aged eight, an obese boy whose asthma had

begun some months before, took the mother doll in his play session, put her in bed and pulled her skirts up. He then pulled the father doll's trousers down and placed him on top of the mother doll. "One day I saw them," he said. "This is what they were doing. I thought they were fighting." Then, getting confused and anxious, he hung his head and began evading, "I saw . . . I didn't see . . . They saw me . . . They didn't!" And right in the play session, he started to cough and wheeze.

When checked, his parents admitted that he had come upon them and that his asthma had begun that night.

In seven children, the first onset of the allergic syndrome occurred after the birth of a sibling. In some of these children there were tentative protests about the newcomer. Said one, timidly, "Send him back to the hospital." Said his mother, "But, he's nice. He's your dear little brother. You don't really want to give him away." Another masked her hostility cunningly under the guise of a caress. "He's so cute," she exclaimed, "I'll eat him up!" And she proceeded to bite the baby, announcing with a smile, "I just wanted to see how good he'd taste." One reverted to baby talk and began to soil and wet. On the whole, their parents reported, "They're so sweet to the baby!" In their play sessions, however, truer feelings emerged. For example, one stuck the baby's head in the toilet bowl, another poured water all over him to make him "not breathe," and another cunningly had the angels take the baby to heaven to live.

Another type of experience preceding the first onset of allergic symptoms can be classed under the heading of over-severe habit training. This sort of episode occurred prior to the first onset of a particular symptom in six cases.

To cite just one example, four-year-old Eddie's mother related that prior to the onset of his asthma several months earlier she had decided she "simply had to" break him of sucking his thumb. "I kept pulling it out of his mouth roughly," she recounted, "and I called him a sissy and told him that big boys don't do that. I showed him how it looked and finally I threatened him I wouldn't love him anymore. Then he had those awful dreams and would get me up at all hours, and the asthma began." Incidentally, he had started to suck his thumb at two years when his sister was born, and although his mother had continuously tried to stop him, the threat of not loving him was the first thing that "worked." In other cases, over-severe and punitive toilet training had similar sequelae.

Another type of episode preceding onset, seen in five cases, can be best categorized as masturbation threats.

To quote one mother of a nine-year-old asthmatic boy, "I caught Lee masturbating when he was about four and a half years old. I was very upset. The doctor said, 'Do nothing.' I couldn't stand it though. I must admit, I threatened him terribly and got furiously angry. About a year ago I told him that it would make it fall off and that he couldn't have any children if he did this. After that he got asthma, and then I told him that doing that would make him wheeze. He confessed a number of times when I asked him what he had done when he wheezed, saying, 'I tickled myself!' "

Another mother had threatened her little two-year-old girl that she would make

TABLE I. TYPES OF TRAUMATIC EPISODES PRECEDING FIRST ONSET OF A PARTICULAR ALLERGIC SYNDROME*

	Cases
Loss or threatened loss of a parent	22
Marital conflict	20
Death in family other than that of parent	3
Witnessing intercourse	4
Birth of sibling	7
Over-severe habit training	6
Masturbation threats	5
Physical violence or threat of violence	7
Surgery	3
Total	77

*French and Alexander[1] have offered a somewhat similar list of emotional factors precipitating attacks of asthma, as follows: (1) sudden intense emotion, (2) crying, (3) sexual conflict, (4) disturbance of a dependent relationship, (5) danger to near relatives, (6) identification with dyspneic attacks of others, (7) secondary utilization of attacks.

herself sore and bleeding and that the doctor would have to get a big darning needle and sew her up. Another said to her two-year-old boy, "If you get your wee hard that way, someday it will get too hard and it will break off." She took a crayon and broke it in two and said, "This way." . . . So as to make him understand.

Closely allied to this, in one instance, was another less obvious episode which apparently held the same meaning to the child. The child had been masturbating and had been told without seeming effect that his penis would come off. Then, one day the father took an animal cracker from him and bit off its leg. The child went into a panic and began to wheeze.

In six cases, episodes of physical violence done to the child preceded the initial onset of allergic symptoms, and in a seventh case, the threat of physical injury. One very rejecting mother lashed her little girl until she was almost unconscious. Another, in a drunken rage, as the father described it, beat her two-year-old "to a pulp." Said another, apologetically, "I'm so ashamed of myself but I couldn't help it. He's so stubborn, I had to beat him until he gave in and cried."

One mother did not engage in physical violence but threatened impending bodily harm to keep her three-year-old from crossing the street. This preceded his first attack of asthma. To use her words, "I scared him witless. I told him there'd be no more John. He'd get squashed under a car."

In three cases, an operation preceded the allergic onset: one adenotonsillectomy, one plastic operation on the hand, and one almost simultaneously executed adenotonsillectomy, circumcision and eye-muscle shortening operation when the child was four. In all of these cases there was inadequate preparation and the children were separated from their mothers preoperatively and postoperatively, being placed where the mothers were not allowed to be with them.

Table I summarizes the foregoing.

DISCUSSION

The incidents which have been related as occurring in the lives of these children are obviously not unique. Many of them occur in some form or other in the life of numbers of children without being followed by any

apparent difficulties. That severe physical illness should have followed in this group can be explained only on the basis that the seed must have fallen on fertile soil—a soil prepared both allergically and psychologically. As far as the allergic preparation is concerned, this goes back essentially to the presence of reagin. But what is the psychological factor?

As the histories of these allergic children are studied in greater detail, and as some of the children reveal themselves more deeply in therapy, the meaning of the episodes cited becomes clearer, so that their traumatic nature is better understood.

When they are seen in context, there emerges one pervasive emotional factor that is common to every type of incident preceding first onset. When one speaks of loss or threatened loss of a parent, the significance is clear. To the child, emotionally it appears that the parent doesn't love him, and in most instances, as has been seen, this means specifically the mother. When marital conflict enters, the child again essentially feels afraid of losing the mother. Death of other members in the family has been seen to generate fear of losing their mother more than anyone else. Witnessing intercourse to the child appears as an attack on the mother and once more activates his fear. Birth of a sibling not only threatens loss but is a realistic loss of part of the mother through the loss of part of the mother's time and attention and, as the child takes it, of her love. To the child, over-severe habit training is in essence as if the mother were saying, "You're not good enough," and this, in turn, is followed by a feeling of not being loved, or, in extreme cases, of being disowned. The masturbation threats mean, "She doesn't love part of me." Physical violence against the child's person bears incontroversial evidence to the child, whereas the mother's leaving him to go alone into the frightening experience of an operation again makes him feel deserted and lost.

These threats have a particularly powerful significance to the allergic child. *They confirm his fear that his mother has never loved him too well.* Nor is this fear unfounded. For, as shown in other studies,[5,6] even though she may not be aware of it, the mother of an allergic child is almost invariably a rejecting mother. As a result, no matter how much care and solicitousness she lavishes on him, he seems to sense her inner attitude. He then feels insecure. And so any episode that appears to him to threaten further loss of his mother may prove traumatic, whereas if he were less insecure, it might not.

Ordinarily when a child feels insecure he becomes resentful and shows it by word or behavior. But it is characteristic of the allergic child that he is unable to bring his resentment out by word or behavior. He characteristically blocks the outgoing expression of his resentment and turns it on himself.[4] He expresses it by using his allergic constitution. His asthma, hay fever or eczema then are his way of saying, "I am angry but I don't dare tell you about it. It scares me to tell you about it. I feel too guilty

about being angry but I have to do something with my anger. I want you to continue loving me, and I'm afraid that if I let you know I'm angry at you, you won't love me at all. So, I get sick."

Usually, all this is done unconsciously.

If allergic children can be helped to get their resentful feelings out in the open, instead of blocking them, they will no longer need to use allergic symptoms so much for this purpose.

In some cases referral for psychotherapy will be indicated.

Where it is necessary to remove the child from the home, not only must the child have psychotherapy but he must also find in the home-away-from-his-home a substitute parent or parents.

In many cases the allergist himself is able to facilitate the emotional care of the patient by his own approach, especially if he has gained psychological orientation. He need not diagnose the where and why of the onset or try to solve the causes of the mother's rejection. He can take the child where he *is*, and by accepting and reflecting the child's feelings, he can help relieve the child's emotional block.

Thus, in the child's presence, a mother starts talking of sending him to boarding school in a better climate. The physician notices the child's bothered expression. He accepts the feelings behind it and reflects them out loud by saying, "It makes you feel sort of mean and mad when mother talks like that."

He can also accept and reflect the mother's feelings. As an example, another mother complains, "I'm all worn out, I need a vacation from him." The physician accepts both her feelings and the child's, and reflects both. He says to the mother, "Sometimes you get so tired you do want to get away from him and from everything. And you," turning to the child, "you get pretty worried and kind of mad, Sonny, when you feel that mother gets that way."

In this way the physician shows that he has understood and has not condemned either mother or child. Both can feel easier. Each can feel inside himself, "Well, I'm not as bad as I thought."

By such an approach, no matter what the onset, the allergist will have shown the patient that he understands him as a person who has emotional as well as physical problems on which he needs help.

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REMARKS ON THE THEORIES OF ANTIBODY FORMATION

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IN THE early days of immunology it was discovered that blood from an animal which had been treated with certain microorganisms would react *in vitro* in a different fashion to the organism in question than would the blood of an untreated animal. Various types of reactions were observed, such as agglutination, precipitation, bacteriolysis, et cetera. It was hypothesized that these reactions were brought about by substances developed by the host in response to the organisms which had beeen introduced. To these substances the generic name of antibodies was given. The nature of these agents was unknown, and they were recognized by their biologic and serologic effects rather than by their physical or chemical properties. During the course of the years a body of knowledge was accumulated which identified the substances possessing such properties with certain serum proteins.

If blood serum is treated with chemical agents such as ammonium sulfate, certain proteins will precipitate out at particular concentrations of the salt. In accordance with these differing solubility characteristics, the proteins have been designated albumin, globulin, pseudoglobulin, euglobulin, et cetera. It has been found that antibodies are largely in the pseudoglobulin and/or euglobulin fractions. More recent study of serum proteins by electrophoretic techniques has shown that the different proteins under the influence of an electrical current have varying mobilities. The protein fractions corresponding to the different mobilities have been labeled albumin, and alpha, beta and gamma globulins. In general, antibodies have been found to be associated with the gamma globulin fraction. Antibodies, then, are serum globulins, which because of an induced physicochemical modification in their structure become capable of mediating certain forms of biological and/or serological activity by which they can be recognized.

At present, the ability to recognize an antibody depends on having a test system by which some function of the antibody can be demonstrated. If a serum or tissue extract is capable of yielding reactions such as those already mentioned, of precipitation, agglutination, et cetera, it is, of course, easy to assert that antibody is present, but it is important to realize that the converse is not necessarily true. If these reactions cannot be elicited, it does not follow that antibodies are absent. It may well be that in certain conditions which are perhaps mediated by antibodies, but in which they have not been detected, the failure is due simply to the lack of an appropriate test system.

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An outstanding feature of all antibodies is their specificity. In other words, an antibody is capable of reacting only with a specific substance which, with few exceptions, is that which originally called forth the antibody. Not all substances can serve as antigens (e.g., evoke antibody), and the exact physical and chemical properties necessary for antigenicity are not yet entirely clearly defined. Suffice it to say that certain molecular aggregates, primarily proteins,* when brought in contact with the body tissues have this property. Certain cells apparently have the capacity to handle foreign protein—to distinguish, as Burnet[6,7] says, "self from not self." The presence of alien protein in the milieu of such cells may cause them to alter (adapt) certain enzyme systems in order to cope with this foreign material. To materials which can cause this enzymatic adaptation to take place we then give the name of antigens. From this point of view the antibody can be regarded as the adapted enzyme system or the new product which arises because of the changed enzyme system acting on its substrate.

As soon as the specificity of antibodies was established, a number of theories were elaborated to account for this phenomenon. Few have stood the test of time. One of the first theories was that of Buchner, who believed that the antibody incorporated antigen or a portion of the antigen into its molecule, thereby deriving its specificity. However, it seems improbable that the very large amount of antibody which can be engendered by very small amounts of antigen could come about from an incorporation of the antigen molecules among the antibody molecules. In addition, when marked antigens, that is, antigens containing a chemically easily detectable substance such as arsenic, are used, it has been found that the antibodies resulting contain no traces of arsenic.

Ehrlich's theory of antibody formation dominated immunologic thinking for many years. Ehrlich hypothesized that certain cells of the body were endowed with a wide variety of preformed "receptors," so constituted that they would specially fit and unite with a given antigen. Under an appropriate antigenic stimulus these cells would manufacture the receptors in such quantities that some would be cast off into the blood stream. These excess receptors were said to constitute circulating antibody. It is difficult to accept the idea that the body should have preformed receptors for the almost infinite variety of natural antigens which it might encounter. It might be argued that over the long phylogenetic history of the human race a sufficiently wide variety of natural antigens had been met, so that receptors for all of them had been formed during the evolutionary process. However, the body is equally capable of forming antibodies to synthetic antigens, which are not met with in nature. Consequently, it is difficult to believe that antibodies are cast off preformed receptors.

*Certain chemicals, e.g. picryl chloride, 2:4 dinitrochlorobenzene, et cetera, are antigenic when applied as such to the skin, but there is good reason to believe that the actual antigen is a conjugate of the simple chemical and a tissue protein. Certain complex polysaccharides are, however, believed to be antigenic in their own right; that is, they stimulate antibody production without first uniting with protein or without containing any protein as an impurity.

It was not until the early 1930's that the first of the modern theories of antibody formation was advanced independently by Breinl and Haurowitz,[15] by Alexander,[1] and by Mudd.[17] In essence the theory proposed by these men is that antigen reaches the site of globulin synthesis where it modifies globulin through a stereochemical influence on the developing protein. In a sense then it may be said that antibody is manufactured in the image of antigen and, consequently, there is a stereochemical correspondence of the one for the other. This theory has been elaborated on by Pauling.[18] While this stereochemical theory adequately explains the specificity of the antibody, certain other aspects of the behavior of antibodies are difficult to reconcile with it. First, it becomes difficult to explain the persistence of sensitivities. If sensitization reactions depend on an antigen-antibody union, then the persistence of the sensitization presumably depends on the continuing presence of antibody in the host. A sensitization may, in some cases, endure many years after the last contact with the antigen, thereby indicating that the antibody has persisted in the host for that time. If, however, the formation of antibody is contingent on the presence of antigen at the site of globulin synthesis, it is necessary to hypothesize that antigen, a foreign material, has persisted as such within the tissues of the host over all these years.

Another phenomenon difficult to explain on the basis of the stereochemical theory is the anamnestic response. The anamnestic response may be described as follows: Following exposure to an antigen, antibody formation begins after a suitable incubation period, rises in titer for a short while, levels off and slowly declines, so that ultimately there is practically no detectable antibody present for the antigen in question. If at this point the animal is given a different antigenic stimulus, not only are antibodies against the new antigen engendered, but there is a recrudescence of the antibodies for the original antigen.† How can this be explained by the stereochemical configurational hypothesis, according to which antigen must be present at the site of globulin synthesis for specific antibody to be produced? The decline of antibody must mean that antigen gradually disappeared from the tissues of the host. If this is so, how does one explain the renewed formation of antibody under the influence of the new and unrelated antigenic stimulus? If, on the other hand, the original antigen did not disappear, how is the gradual cessation of antibody formation after the original antigenic stimulus to be explained?**

The most recent theory of antibody formation is that introduced by Burnet.[6,7] Like Breinl and Haurowitz, Burnet believes that antigen must reach site of globulin synthesis, but does not hold with the idea that the antigen molecule remains as a scaffold or framework about which anti-

†In the very recent literature (see E. E. Fischel et al: J. Immunology, 61:89, 1949), there seems to be doubt as to whether a heterologous antigen can evoke an anamnestic response. There is no doubt that a homologous antigen can call forth a more rapid and abundant antibody response.

**Hypotheses could be constructed which would reconcile the anamnestic response with the stereochemical configurational hypothesis, but in view of their completely speculative nature, we do not feel that a recital of them would at this place be profitable.

body molecules are synthesized. His concept is that antigenic protein causes antibody production through a modifying effect on intracellular proteinases, which are responsible both for the destruction of protein and for its intracellular synthesis.

We should like to elaborate on this theory, as we believe it to be the one that most closely approximates reality. Some of the concepts on which Burnet's theory is based are relatively new and are related to recent advances in knowledge of the chemistry and reproduction of the living cell. These concepts are concerned especially with modern theories of enzymatic adaptation and of cell replication. All cells are endowed with enzyme systems, capable of causing certain biochemical changes on appropriate substances (the substrate), so that they can be utilized in metabolism. For example, the appropriate enzyme system will, say, on one hand, cause sucrose to break down into its constituent monosaccharides and, on the other, cause proteases to hydrolyze proteins. In the presence of certain substances some cells can adapt so as to utilize or act on substances which they originally were powerless to attack, by modifying their enzyme systems. This phenomenon has been studied in detail in the case of carbohydrate-splitting bacteria. Strains of B. coli which are at first unable to ferment lactose will develop lactose-splitting ability after a period of time in contact with this substance. There is a time lag in the ability of the cell to acquire this enzymic ability, but once the adaptation has occurred, the descendants of these cells are able to handle the new substrate on first contact with it. This means that the enzymatic adaptation has been passed along to the daughter cells or, in other words, it has been inherited. It is not known with certainty how this inheritance is achieved, but there is evidence that in the course of enzymatic adaptation cytoplasmic self-duplicating units are formed, which in cell division are distributed to daughter cells and thereby transmit the newly acquired ability from cell to cell.*

It should be pointed out that Sabin[19] on the basis of her studies with a colored antigen (R-salt-azo-benzidine-azo-egg albumin) has also come to the conclusion that antibody formation is related to cytoplasmic alterations in the macrophages. Quoting from Sabin:

"The hypothesis which may be formulated from these observations is that the cells of the reticuloendothelial system take up foreign materials which may be classified into two groups, namely, antigens and non-antigens. Both kinds of material are first taken into the vacuoles of the cells, indicating that a cell guards its basic cytoplasm from the immediate entrance of foreign substances. The vacuoles are the cellular organs of digestion; the cytoplasm is the zone of syntheses. In turn, the synthesis of cytoplasm is usually from normal food substances. If the material phagocytized is an antigen, it is rendered into suitable soluble form within the vacuole and then passed into the cytoplasm itself. There its presence in some way increases the synthesis of globulin and modifies some of it into antibody globulin. Thus, an antigen may be defined as a substance which can specifically modify the synthesis of cyto-

*In this connection, it is of interest to note that Billingham and Medawar[2,3] postulate a similar mechanism for the "infecting" of white skin by black skin in autotransplantation experiments in guinea pigs.

plasm. This process is the evolution of a change in cytoplasm in response to environment. It may be possible that the cell which has formed a new kind of globulin and still retains it in the cytoplasm is sensitized, meaning that it would react differently from the normal cell in the presence of the original antigen."

She, as the quotations clearly indicate, envisioned an intracellular cytoplasmic alteration which yielded the antibody, yet she proffered no explanation as to how the presence of the antigenic protein achieved the alteration in globulin synthesis. Nowhere does Sabin mention the concept of enzymic adaptation.

At this point it would be natural to inquire as to the evidence which links antibody formation with enzymatic adaptation. It is freely admitted that there is no complete proof that these two phenomena are connected, yet what evidence there is, is not at variance with such a hypothesis. Before considering this evidence, it should be pointed out that all known enzymes are proteins. Fagraeus[12] found that during the course of immunization plasma cells increase at the time antibodies are being manufactured and that nucleoprotein is found in the cytoplasm of these cells. Harris and Harris[13] observed that in lymph nodes actively engaged in the production of antibodies a wide range of lymphocytes, largely younger forms, was found to have cytoplasmic granules and that their nuclei stained with pyronine, which is used to identify ribonucleic acid. It had been previously shown by Caspersson[10] and Brachet[5] that cells which were actively forming new protein were characterized by large amounts of ribonucleic acid in their cytoplasm. Bing[4] and others have shown that when a hyperglobulinemia exists, the number of plasma cells is increased, suggesting that the plasma cells manufactured globulin. Spiegelman and Kamen[20] came to the conclusion that (1) genes continually produce at different rates partial replicas of themselves which enter the cytoplasm, (2) these replicas are nucleoprotein in nature and possess to varying degrees the capacity for self-duplication, (3) their presence in the cytoplasm controls the type and amount of protein synthesis and of enzyme formation. Experiments by Cannon[8] indicate that protein depletion brings about an impaired ability on the part of the animal to manufacture globulin and to produce antibodies in response to an antigenic stimulus. The giving of adequate supplies of protein causes the serum globulin level to rise to normal levels and restores the antibody producing capacity of the animal to the full. Similarly, experiments reported by Virtanen[21] show that a decrease in the nitrogen content of the culture medium inhibits saccharase production by B. coli. For this organism saccharase is an adaptive enzyme, formed by previous contact with the corresponding carbohydrate. It would thus appear that both enzyme adaptation and antibody formation occur only under conditions of protein synthesis and at such times nucleoprotein is laid down in the cytoplasm of the cell.

The question of the site of antibody formation has long been under study. For quite some time it was realized that the reticuloendothelial

system somehow participated in antibody formation, and a considerable number of experiments were carried out in an endeavor to clarify its role in this process. Early workers tried by extirpating certain tissues to assess the role of each in antibody formation. Suffice it to say that such experiments failed, for as is now realized antibody formation is not a function localized to a certain tissue or organ. The next step was to attempt to block the reticuloendothelial system, using various techniques. The results of such experiments were on the whole conflicting. Cannon[9] has shown that if reticulo-endothelial blockade is sufficiently complete and kept up long enough, a depression of antibody formation results, but with incomplete blockade there is either no effect on antibody formation or an apparent enhancement. Attempts have been made to determine the site of antibody formation by making extracts from different organs to determine whether antibodies could be found earlier or in larger quantities in these extracts than in the serum.

McMaster and Hudack,[16] using two different bacterial suspensions as antigens, found that if one antigen was injected into one ear of the experimental animal, and the second antigen into the other ear, the highest titer of agglutinins for each organism was found in the lymph nodes which drained the ear into which that organism had been placed. The concentration of agglutinins for the corresponding antigen was least in the lymph nodes of the opposite side and the concentration in the serum stayed somewhere between the two. This result seems to indicate that the agglutinins were formed in the node draining the area into which the organisms had been injected.

Similar work has been carried on by Ehrich, Harris[11] and their coworkers, showing that in rabbits after injection of antigenic material into the leg distal to the popliteal lymph node, specific antibodies were found first in the node itself or in the lymph channel leading from it. The lymph in the afferent lymph channel did not contain any antibody. It seems then reasonably clearly established that lymph nodes participate in antibody formation, although these experiments do not exclude antibody formation in other parts of the reticulo-endothelial system. As a result of her studies with a dye antigen, Sabin[19] concluded that "for the experimental production of antibodies one may call into action either the tissues of the liver and spleen by employing the intravenous route of injection, or local macrophages and the endothelium and macrophages of the regional lymph nodes." It appears then that antibody manufacture is a function of cells of the reticulo-endothelial system, whether localized in a viscus as the spleen, or a lymph node, or distributed diffusely as in the true cutis. Hartley,[14] for example, has shown by the production of cutaneous nodules which consisted largely of macrophages that if a virus was introduced into such a nodule, antibodies could be detected earlier in extracts from it than in serum or in extracts from any other tissue.

Since the reticulo-endothelial system is not a homogeneous system of cells, one might inquire whether all the cells or only certain of them have antibody-forming powers. Sabin's studies showed that antigenic material is engulfed by macrophages and by neutrophilic leukocytes, and the appearance of antibodies in the serum coincided with the disappearance of dye protein in macrophages and with partial shedding of the surface films of these cells, indicating that these are concerned in antibody formation. The histochemical studies by Harris and Harris of lymph nodes actively engaged in producing antibodies have already been alluded to. These investigators point out that the only cell types in which there was evidence of new protein formation was in young lymphocytes and in transitional forms between reticulum cells and lymphocytes, but in no other cell types. They specifically state that no plasma cells were seen in the greatly enlarged cortex of the stimulated nodes, and the few plasma cells seen in the medullas were similar in number and location in both the control and the stimulated nodes.

Recent work by Scandinavian workers led them to the belief that plasma cells are the cells which actually elaborate antibodies. On the basis of extensive studies Fagraeus[12] came to the following conclusions: (1) repeated injections of antigen (ovalbumin) yield an evident plasma cell reaction, (2) the plasma cells do not increase after injections of non-antigenic substances or after passive immunization, (3) a clear correlation can be made between the appearance of plasma cells and antibody titers. She goes on to say, "the particular type of cells that have been interpreted here as immature forms of plasma cells in earlier investigations have been given various names, such as lymphoblasts, large basophilic cells, monocytic cells and so on. The present author has preferred to call these reticulo-endothelial elements immature plasma cells, in view of the fact that most of them, with the immunization technique that has been applied, develop into plasma cells. Some authors would, no doubt, assign them to the series of lymphocytes."

We should like to point out that it is possible to reconcile these various somewhat divergent experimental findings and weld them into one homogeneous scheme. Most authorities agree that the primitive reticulum cell or undifferentiated mesenchymal cell gives rise to a wide variety of cells, which include among others macrophages of various kinds, plasma cells, and lymphocytes. This being so, much of the argument as to the precise cell which engenders antibody is meaningless, inasmuch as all are derivatives of the same cell, and the predominating cell can vary with such secondary factors as the nature of the antigen, the route of administration, et cetera. Such a concept has even a more profound significance in light of Burnet's views. If it is hypothesized that the enzymic adaptation takes place in the primitive reticulum cell, the persistence of specific sensitization for periods considerably longer than the lives of individual lymph-

ocytes or plasma cells can be explained. If the antigen causes the enzymic alteration to take place in the primitive reticulum cell, the alteration can then be passed on to the descendants of this cell, such as lymphocytes and/or plasma cells. Assuming these cells synthesize globulin, they would now synthesize an altered globulin (the antibody) because of the inherited enzyme modification, originally induced by contact with antigen. The specificity of the antibody would be against the antigen which caused the adaptation in the enzyme system of the reticulum cell. Thus, it would not be necessary to provide evidence that the actual antibody manufacturing cells themselves came into contact with or somehow utilized the antigen. Defined according to this concept, an antigen is a substance which when picked up by the cells of the reticulo-endothelial system is capable of causing in them an enzymic adaptation, which may then be transmitted to their descendants by cytoplasmic factors. Whether the enzymic adaptation can take place in any of the cells of the system or only in certain ones is not known, but it would not be necessary that the original adaptation take place in any cell other than the primitive reticulum cell. As a consequence of this enzymic adaptation, certain metabolites of the involved cell are altered. If the metabolite is a serum globulin, then that globulin will have modifications in its structure which will enable it to yield the biologic and serologic reactions given by the substances we call antibodies.

In discussing the stereochemical configurational hypothesis we pointed out the difficulty of reconciling the persistence of sensitizations and the anamnestic response with such a theory. With the enzymic adaptation theory these difficulties are obviated. First, it becomes unnecessary to postulate that antigen persists as such at the sites of globulin synthesis for long periods of time, and one need only assume that cellular inheritance of the enzymic adaptation occurs. The evidence for this point has already been given. Second, since any stimulus which would cause proliferation of cells which altered enzymatic capacities would result in increased liberation of the specifically modified globulin, the recrudescence of antibody under a heterologous antigenic stimulus (as in the anamnestic response) is explained. The prompt and rapid formation of antibody upon renewed contact with the original antigen is even easier to explain. In this case the enzymic alteration has already been effected at the time of the original contact. It is lying dormant, so to speak, awaiting more of the appropriate substrate, and as soon as the cell encounters this it can immediately utilize it with the more or less immediate elaboration of antibody.

We regard the intracellular enzymic adaptation as the essential response to antigen; whether or not as a consequence of it a modified serum globulin is released is in a sense an antigenic accident. In the tuberculous and eczematous types of sensitization† no antibodies can be found in the

†In deference to current usage, we are referring to the tuberculous and eczematous types of sensitization as if they were distinct immunologic entities. However, it seems to us that it is likely that the eczematous sensitization is a variant of the bacterial (tuberculin) in which the full antigen is manufactured in the epidermo-cutis and, consequently, the major reactions of this sensitization are seen in that tissue.

serum; yet certain cells (lymphocytes, macrophages) have acquired new properties towards the antigen as shown by tissue culture experiments and passive transfer experiments. We suggest that in these cells there has been an enzymic adaptation but since in this case the enzymes involved do not have to do with globulin synthesis, there is no modification in the serum globulin, and, consequently, the alteration is not detectable by means of the usual serum reactions; however, when these cells again meet the antigen, they react to it in a different fashion than does a cell with an unadapted enzyme system. Of course, it is possible that the antigens which elicit these types of sensitization actually affect different cells than do the antigens which engender the anaphylactic type of sensitization, but there is no evidence to support such a view, and there is some evidence that the same types of cells are involved. Consequently, the more likely hypothesis is that different enzyme systems can be affected according to the nature of the antigen.

Assuming this point of view to be correct, a point of nomenclature is raised. With current thinking, it is customary to refer to sessile or tissue-fixed antibodies in the tuberculin and eczematous sensitizations. To us, the specificity found in these states is contingent on the specifically sensitized cells with stereochemically (?) altered enzyme systems. An antibody is a globulin whose synthesis has been modified as a result of an enzymic adaptation. This antibody can exist freely in the tissues of the body or can be attached to certain cells. Many, if not all, antibody functions can be shown apart from the cells which elaborate them; in the case of the sensitized cells of the bacterial sensitization so far at least the manifestations of the sensitization are inherent to an intact living cell and cannot be divorced from it.

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(Continued on Page 148)

CLINICAL EVALUATION OF THENYLPYRAMINE HYDROCHLORIDE (HISTADYL) IN THE TREATMENT OF ALLERGIC SYMPTOMS

EMANUEL SCHWARTZ, M.D., F.A.C.A., LOUIS LEVIN, M.D., F.A.C.A., and MILTON WALLMAN, M.D.

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EVER since it was demonstrated in 1933 by Fourneau and Bovet,[4] and in 1939 by Staub,[10] that the effects of histamine in the animal body could be nullified by certain phenolic ethers, there have been a great number of similar compounds produced in our country and abroad. Because of the marked toxicity of the phenol ethers, attention was soon given to a group of related compounds in the Fourneau series with the ethylene diamine radical. From this radical were evolved the now familiar antihistaminic agents, Benadryl, Pyribenzamine, Neo-Antergan, and numerous others. Various investigators[1,2,6,7,9] working with these drugs reported more or less similar good results for all of them. However, they all gave some degree of toxic reactions, much less than the older original compounds, but nevertheless in sufficient amount to warrant discontinuation of the drug in numerous instances. Another observation was that these drugs did not continue giving the same results all of the time. The very same patients who would obtain relief at one time would not do so at other times with the same drug, and in many instances would get relief from another type of similar drug. Also, there were many patients who would fail to obtain relief initially from one of the drugs but would not do so from another of similar nature. This led to further search for newer compounds so that more patients could be brought into the fold of those obtaining relief.

Among the newer antihistaminics that contain this ethylene diamine radical is thenylpyramine hydrochloride or Histadyl. As can be seen at a glance, it is closely related to Benadryl and Pyribenzamine.

PHARMACOLOGY

Pharmacologic investigations carried out by Feinberg and Bernstein,[3] Roth, Richards, and Sheppard,[8] and Lee and Dinwiddie[5] indicate that thenylpyramine, or Histadyl, is generally as effective as the other well-known antihistaminics in preventing anaphylactic shock in guinea pigs treated with histamine.

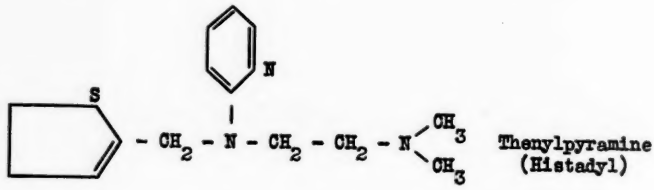
CLINICAL FINDINGS

A series of eighty-nine cases were treated with Histadyl. The cases were chosen without any regard to the severity of the symptoms. All cases of hay fever, asthma and vasomotor rhinitis received routine injection treatment along with the antihistaminic. The Histadyl was given in doses of 50 mg. three times daily. In those instances where there was no relief and there were no severe toxic reactions, the dose was increased to 100 mg. three times daily.

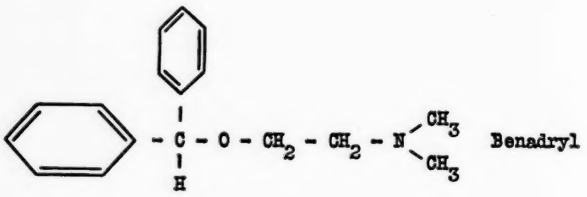
From the Division of Allergy of the Department of Medicine of The Long Island College Hospital. Histadyl was furnished through the courtesy of Ely Lilly & Co. Dr. Milton Wallman is an Associate Fellow of The American College of Allergists.

TABLE I. RESULTS OF TREATMENT OF PATIENTS WITH HISTADYL

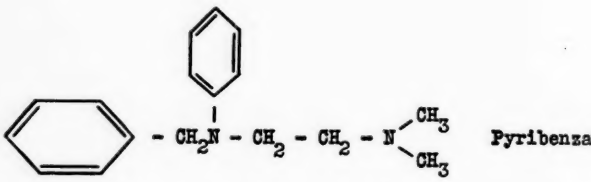
Allergic Disease	Number of Cases	Relief	No Relief	Percentage Relieved
Hay fever	47	36	11	76.6
Vasomotor rhinitis	17	9	8	53.9
Bronchial asthma	13	2	11	15.4
Chronic urticaria	3	2	1	66.6
Allergic eczema	2	1	1	50.0
Acute urticaria	5	4	1	80.0
Contact dermatitis	2	1	1	50.0
Totals	89	55	34	61.8



Thenylpyramine (Histadyl)



Benadryl



Pyribenzamine

The accompanying tables show the symptomatic results and the toxic reactions obtained in this group of patients. Table I evaluates the percentage of patients with hay fever, bronchial asthma, et cetera, who obtained relief from this drug. Relief usually occurred in one-half to one hour after ingestion of the drug, although sometimes three or four doses had to be taken before relief was obtained. As has been observed with other antihistaminics and previously mentioned, about one-third of the patients obtained relief at one period of time with the medication and no relief at another. This occurred at any time during the treatment. Relief lasted from three to six hours after a single dose of the drug. In tabulating our results, all persons who did not claim considerable relief were regarded as "no relief."

TABLE II. HISTADYL (89 CASES)—SIDE REACTIONS (18 CASES—20%)

Side Reaction	No. of Cases
Drowsiness	9
Dizziness	2
Dryness of mouth	2
Nausea	3
Abdominal cramps	2
Weakness	1
Palpitation	1
Tiredness	1
Nervousness	2

Toxic reactions occurred in eighteen (20 per cent) of the eighty-nine cases. The type and frequency are listed in Table II.

DISCUSSION

Our best results were obtained with the hay fever cases (76.6 per cent relief) and with cases of vasomotor rhinitis (53.9 per cent relief). Although the results in bronchial asthma were not as good (only 15.4 per cent relief) as those observed with several other antihistaminic drugs, it would not be fair to draw any conclusions from the small number of cases (thirteen) in this listing. The same holds true for the skin conditions listed.

Toxic reactions occurred in 20 per cent of the cases. Drowsiness and gastrointestinal symptoms were the most common side effects encountered. The drowsiness was seldom severe enough for us to discontinue the drug.

In all of the cases the benefit derived from Histadyl was only temporary and ceased when the patient discontinued its use due to lack of medication or carelessness.

CONCLUSIONS

Histadyl, a synthetic antihistaminic compound, was used in the treatment of eighty-nine cases with allergic manifestations. In doses of 50 to 100 mg. it afforded relief in the majority of the seasonal and non-seasonal allergic rhinitis cases. These results compared satisfactorily with the action of other antihistaminics. Side effects are less frequent than with Benadryl, but about the same as with Pyribenzamine, especially as to the leading toxic symptom, which seems to be common to most of the antihistaminics, namely, drowsiness.

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PULMONARY FIBROSIS COMPLICATING ALLERGIC ASTHMA

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THE following case of bronchial asthma is presented because it offers certain unusual clinical and pathological features, the most significant being the fact that a psychosomatic trauma appeared to be responsible for death.

CASE REPORT

Mr. J. L. H., forty-six years old, was seen in September, 1948. He had just returned from a four months' stay in Arizona, where he had sought relief from chronic intractable asthma with which he had been afflicted for twenty years. There was an allergic family background and a history of frequent nasal and bronchial catarrhs, of croup in early childhood, and hay fever since 1925. The asthma had been present for ten years, at first confined to the grass pollen season and since 1946 assuming a perennial and persistent course. During the past six months the patient had become greatly debilitated, spending much of his time in bed, with dyspnea on the slightest exertion and with changes of temperature. Ever since he was skin tested eight years ago, he had strenuously adhered to an elimination diet, avoiding, to the point of fear, such foods as chicken, turkey, nuts, eggs, milk. In Arizona, he experienced slight relief from May through August. Since then he had had constant dyspnea. His treatment up to this time had consisted of practically all known medications for asthma, including sulfa drugs and penicillin, with emphasis on strict elimination of offending foods, with habitual use of the epinephrine spray as well as self-administration of epinephrine injections.

On physical examination, the patient was about 15 pounds underweight; there was relatively little cyanosis. There was a peculiar type of breathing which might be described as air hunger, both inspiratory and expiratory. Except for some wheezing in the tracheo-bronchial area, very few rhonchi were heard. The lower portions of the lungs appeared to be rigid, the breath sounds being hardly audible, and there was marked hyper-resonance, which was somewhat suggestive of pneumothorax. It was noted that the wheezing ceased entirely as soon as the patient's attention was drawn away from his ailment. In spite of the history of chronic sinus catarrh, the nose and sinuses were clear on transillumination and on x-ray examination. The heart rate ranged between 90 and 120; the sounds were faint but clear. The white blood count was within normal limits, the eosinophiles ranging up to 12 per cent. The sputum was nonpurulent. A bronchogram showed emphysema, evidence of an apical pleurisy and an arrested lesion in the right apex. Lipiodol did not reach the peripheral portions of the lungs (Fig. 1). A therapeutic bronchoscopic lavage ten days later (Dr. J. Birch), indicated that this was due to marked spasm in the secondary bronchi; there was practically no mucus in the bronchi. There were otherwise no noteworthy findings.

Intradermal skin tests revealed numerous 1 to 3- plus reactions to all types of antigens. The following inhalants were considered clinically significant and selected for hyposensitization: short and long ragweed, English plantain, timothy, June grass, Monilia, smut, Hormodendrum and Endo house dust. In addition he was given hyposensitizing injections for milk and egg.

After futile attempts at relieving the patient at the office, he was hospitalized on September 13. He was given a 2800 calorie diet, disregarding all food sensitivity,

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four daily injections of the above named pollen and inhalants in gradually increasing doses, and three blood transfusions. On this regime the patient improved steadily. It was possible to discontinue all symptomatic medication. He was ready to be discharged

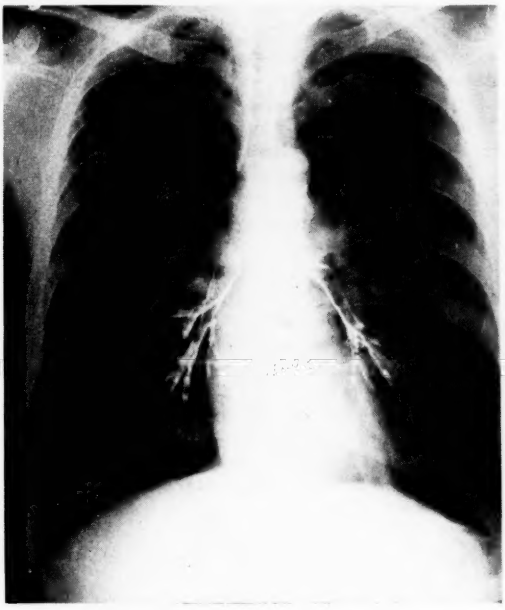

Fig. 1. Bronchogram showing obstruction of bronchi in lower portions of lungs. Bronchoscopy revealed marked spasm in the obstructed areas and no mucous plugs.

on the fifth hospital day. At the instant when his wife entered the hospital room to take him home, he developed severe dyspnea, resulting in an asthmatic attack which lasted for two hours.

Because of this and other psychosomatic features, it was attempted to obtain further data on his background. The patient had lost his father at the age of eight and had to work hard ever since in order to secure a livelihood for himself and his mother. He had seen two members of his family die from asthma and had always been told by doctors as well as by his family that asthma is incurable. He suspected his heart to be failing because a doctor once told him that he had low blood pressure. The fact that several electrocardiograms had been entirely normal failed to allay his worry on this score. Most therapeutic measures which he had tried relieved him at first for a few days only and then lost their beneficial effect. His wife treated him as an invalid, waiting on him on every occasion. She had to dress and undress him daily, a procedure which took at least forty-five minutes. He greatly resented her insistence on assisting and babying him, a fact which led to daily arguments with her. His wife's family had objected to their marriage on religious grounds. He frequently indicated that he "hated" his son. He felt very insecure in his job. While being well-liked by his fellow workers and superiors, he was in constant fear that he would lose his job and thereby his only chance of making a living. Nevertheless, his employer was personally interested in him, to the extent of paying his medical expenses

for over a year and a half. At no time within the past ten years had he gone to bed without taking some medication, usually large doses of epinephrine and barbiturates. Yet, he never slept more than one or two hours at night, and had to catch up on his sleep during the morning and noon hours. The noise made by the children of his upstairs' neighbor interfered with this routine and constituted a source of annoyance to him.

Much time was spent in convincing him that only very few patients die from asthma and that his case was curable. His wife was advised that her excessive attention was harmful to him. With the aid of placebos, we succeeded in eliminating sedatives and epinephrine. He was soon able to dress himself and managed to take daily walks outdoors and other light exercise. His asthma improved to such an extent that the minor attacks following exertion began to subside. He made daily visits to his office in the morning, spending the afternoons at the clinic where he was given hyposensitization treatment and where his problems were discussed with him. There was a gain in weight of 5 pounds. Two minor set-backs in late October, probably due to upper respiratory infections, responded well to treatment with penicillin.

About the early part of November, eight weeks after he was first seen, for some unknown reason, the attacks became more severe. After the usual symptomatic therapy had failed, he was referred to a psychiatrist (Dr. L. C. Foster) who brought out the following additional facts: There had been an extreme hostility of the patient's mother towards him practically throughout his whole life. When he was born, she expected a girl instead of a boy and she seemed to hold this mistake of Nature against him throughout his life. She did not wish him to marry and did not wish him to have children. Whenever he spoke about his mother he became flushed, excited, threw back his head and started his labored breathing. The psychiatrist considered his wife's overprotective and maternal role towards her husband another major issue. It made the patient assume the attitude of invalidism very early in his illness. The patient was very eager to discuss his affairs and wished to "evacuate" all his problems to the psychiatrist.

After the first appointment there was immediate improvement in the patient's general condition. About November 18 he again developed an upper respiratory infection associated with slight fever, marked wheezing, expectoration of purulent sputum, and a leukocytosis of 23,000. There was some edema in his ankles. The pulse rate ranged between 110 and 120. He was again given procaine penicillin in daily doses of 300,000 units for ten days. The fever and general malaise subsided but the asthma was very difficult to control. He resumed some of his previous medications, including the epinephrine spray. On November 29 a short interview with the psychiatrist benefited him materially. The following day he was to be seen again by the psychiatrist, but after waiting in my office for several hours he was told the appointment for this day had to be cancelled. I, therefore, attempted to reassure him and to relieve his tension, promising him that he would be seen by the psychiatrist on the following day.

On the morning of December 1, he was given an injection of 300,000 units of penicillin, and two hours later an intravenous injection of one-third of the 3¾ grain ampoule of aminophylline. His general condition seemed satisfactory. Having again failed to meet with the psychiatrist at the appointed hour in the morning, he continued to wait for him in my office. At 3:00 p.m. I was notified that through some misunderstanding the psychiatrist once more had to postpone the appointment. When the patient was given this message, he instantly became pale, broke out in cold perspiration and developed general collapse. His pulse rate rose to 220, the systolic blood pressure dropped to 65 over 30. He began to gasp for breath. Two c.c. of caffein sodium benzoate failed to improve him. As his condition gradually deteriorated, he was hospitalized. The admitting house officer gave him 1.0 c.c. of Digalen intravenously, 3¾ grain of aminophylline, and 1/10 c.c. of epinephrine. The cardiologist's

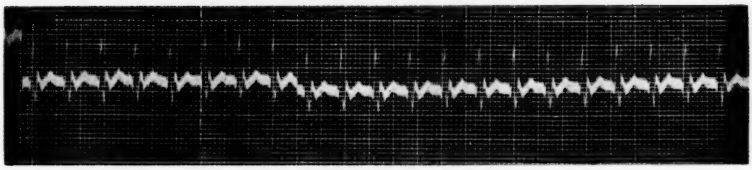

Fig. 2. Electrocardiogram showing supraventricular tachycardia probably of nodal origin. (Only one lead was taken because of technical difficulties.)

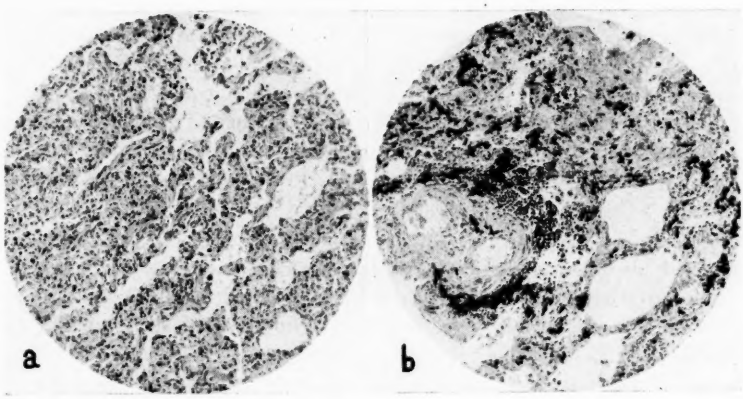

Fig. 3. Microscopic sections of lower lungs showing marked interstitial fibrosis (a) and peribronchial inflammation (b) and ruptured alveoli.

examination (Dr. W. Cooksey) revealed a moderate degree of dyspnea but very little cyanosis. There were no râles and no rhonchi. The heart sounds were faint but clear. His diagnosis was acute paroxysmal tachycardia. The electrocardiogram (Fig. 2) at this time tended to confirm this diagnosis. There was no response of the pulse rate to carotid pressure. The patient was given 3 grains of quinidine, and the orders for further doses of epinephrine and digitalis were discontinued. The patient gradually deteriorated and expired at 9:00 p.m. As cause of death, the cardiologist considered "myocardial exhaustion" and felt that ventricular fibrillation, possibly aggravated by the single dose of epinephrine and the intravenous digitalis might have been a terminal feature.

The autopsy showed no pathologic lesion in the upper lobes of the lungs other than emphysema. In the lower portions there were several emphysematous blebs. There was no mucus in the trachea or the bronchial tubes and no inflammation of the bronchial mucosa. The heart was entirely normal in size and appearance, the liver slightly enlarged. There was some ankle edema and some passive congestion in the kidneys, liver and spleen.

Microscopically the upper lobes of the lungs appeared normal. The sections from the lower lobes (Fig. 3) exhibited marked interstitial fibrosis, some hypertrophy of the bronchial walls and peribronchial inflammation. The pathologist believed that death was due to paroxysmal tachycardia and that the fibrosis in the lungs represented a complication of allergic asthma but had no bearing on the cause of death.

DISCUSSION

The allergic history, the positive response to skin testing, and the eosinophilia definitely establish the primary diagnosis of allergic bronchial asthma. However, at autopsy the cardinal findings of asthmatic death, namely, the presence of thick tenacious mucus in the bronchi, were lacking. There was thickening of the bronchial musculature as well as some foci of leukocytosis and eosinophilia. The thickening of the bronchial musculature might have resulted from persistent spasm which may or may not have been aggravated by his psychosomatic state. The peculiar type of breathing and complete lack of aeration in the lower portions of the lungs noted on auscultation and suggested by the bronchogram was explained at autopsy by the uniform fibrosis of large portions of pulmonary areas in the lung bases which were evidently completely eliminated from respiratory function. Such fibrosis which resulted in formation of ruptured alveolar blebs has not been stressed as a major finding in allergic asthma.

The most striking feature was the mode of death. The patient had not been in a critical condition until the psychic trauma occurred, namely, the disappointment of not being seen by the psychiatrist. This did not, as to be expected, elicit an asthmatic seizure but a true case of paroxysmal tachycardia corroborated by electrocardiographic evidence. Practically no wheezing was present when the patient was lying flat in bed. There was no indication of anaphylactic shock, such as pulmonary edema and petechial hemorrhages of the lungs and other organs, nor was there evidence of cardiac damage at autopsy. It is well known that death may be precipitated by a psychic stimulus and that the autopsy in such instances does not give any clue whatsoever of the immediate cause of death. In our case there was clinical and pathological evidence of a major inhibition in respiratory function which may have been sufficient to account for death.

SUMMARY

A patient with chronic allergic asthma susceptible to marked psychosomatic aggravation contracted the clinical syndrome of paroxysmal tachycardia following a psychic trauma. This was associated with severe shock and followed by death. The autopsy failed to establish the cause of death, the heart being of normal appearance and the characteristic findings of allergic asthma being absent. Instead, the lower portions of the lungs exhibited fibrosis and ruptured alveolar blebs.

10 Peterboro

DISCUSSION

MILTON M. HARTMAN, M.D., San Francisco: I believe that the title of "An Unusual Case of Asthma with Fatal Termination" would be a more accurate designation for the excellent case description that Dr. Waldbott has just presented. There appears to have been ample organic cause for exitus without bringing in a psychosomatic factor. The emotional state certainly can modify or aggravate the physical reactions of an individual with the allergic constitution, but only if serious organic damage is present can the balance be tipped in favor of the Grim Reaper. The basic reflexes in

the unconscious stratum are directed toward self-preservation, and in a showdown outweigh any immediate tendencies toward self-destruction resulting from conflicts in the subconscious. Even conscious desires for self-destruction are nullified except in the presence of a definite psychosis. Few who have committed suicide could be considered sane.

The current fashionable swing of the medical pendulum to psychosomatic medicine has unfortunately resulted in labeling any disorder for which no immediately obvious inflammatory, neoplastic, metabolic or traumatic cause can be found as "psychosomatic." This is most unfair to allergic disorders, for their causes are only infrequently obvious, and painstaking investigation is usually required.

Death from bronchial asthma uncomplicated by pre-existing renal, heart, or suppurative lung disease should be a rarity. When it does occur there must be a definite anatomic or physiologic cause. The discussor's investigation of deaths from "uncomplicated" asthma in the San Francisco Bay region (1943-1948) which led to his studies on water and electrolyte disturbances during status asthmaticus revealed the following causes of death:

Acute myocardial infarction	3 cases
Spontaneous pneumothorax	1 case
Morphine administration	7 cases
Bronchial and bronchiolar obstruction from mucous plugs	4 cases
Dehydration	5 cases
Hypopotassinemia (consequence of improper hydration following starvation and dehydration)	6 cases
Total	26 cases

Needless to say, access to many case records was impossible to obtain. Note that the deaths in only the first two categories were unpreventable. More publicity regarding the effect of morphine upon asthmatics will eventually end that menace. Deaths in the last three categories are preventable by bronchoscopy with aspiration, adequate prophylactic hydration, and by corrective hydration under laboratory control. I may add that three of the deaths due to respiratory muscle paralysis from low plasma potassium had been considered "psychosomatic." To one familiar with the clinical course and electrocardiographic changes of such cases, the reason for exitus was obvious from the case histories.

COTTONSEED PROTEIN VS. COTTONSEED OIL SENSITIVITY

(Continued from Page 22)

study of food allergy may be adopted by others in order that our knowledge of this disorder may be enhanced.

The author wishes to acknowledge with thanks the technical help of Misses Gloria Seeberg and Cecilia Spearing.

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EPINEPHRINE IN THE TREATMENT OF MIGRAINE

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THE ETIOLOGY of migraine has not been definitely settled. The most acceptable theories of this syndrome consider the factors of heredity, allergy, and endocrine disorders. A realization of the personality types involved and their reactions to the stresses and strains of life is important.

Most authorities believe that the essential pathologic physiology consists of a period of cerebral vasoconstriction followed by vasodilation. The headache is thought to be due to the latter. Ergotamine tartrate is probably the most useful drug in the treatment of migraine. It is believed to act by constricting cranial arteries. The unpleasant side effects of the drug are supposed to be reduced by the new derivative dihydroergotamine.

It is the purpose of this paper to present the results attained with the use of epinephrine and to gauge its effectiveness as compared with ergotamine.

A severe case of migraine which had never responded to any type of medication previously used prompted this investigation. The patient felt "her head was going to explode" from internal pressure and she begged for relief. Her symptoms were thought to be due to extreme vasodilation. Cautiously a small dose of epinephrine was given to observe its effect and see if we could secure vasoconstriction. The dose was .012 c.c. or 1/80 c.c. of 1:1000 aqueous solution given subcutaneously. Almost complete relief followed within five minutes. A second injection of the same dosage cleared the headache.

About one month later the patient returned with a new attack. She again quickly responded to the drug. It was suggested that she try ephedrine orally the next time she had migraine. Upon her following visit she stated that the latter medication had very little value and she wanted Adrenalin.

This patient was a thirty-year-old married woman with domestic, marital, and family difficulties. There was no allergic history nor was there any correlation between foods and the attacks. Migraine had been present for about ten years. It started with a unilateral headache which soon became generalized. There were visual disturbances, nausea, and emesis. No method of therapy previously used had any effect on the syndrome. The patient would recover after two or three days. Demerol or morphine would give temporary relief from the headache, but the migraine would run its usual course. Epinephrine on three successive occasions stopped her attacks. The first one was about twenty-four hours' duration, the others were about six hours in length.

The second patient was a forty-five-year-old married woman who was working as a domestic to support her husband and son. She was intelligent and formerly was a typist but was now unable to compete with younger workers She disliked her job. Her family was a distinct problem. Migraine was brought on by emotional conflicts, family quarrels. In addition, chocolate, peanuts, and cheese initiated headaches.

The patient was observed in about ten different episodes. They varied from about one-half hour to twenty-four hours in length. If used early in her attacks, ergotamine either orally or subcutaneously in 5 to 10 mg. dosage

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gave relief. The same was true of epinephrine in 0.25 c.c. injections. With either drug the migraine was helped for about one-half to one and one-half hours. If the attack was mild, it would soon terminate; if severe, it would require re-administration of the particular medication used. Sometimes, if too severe, neither drug would help. If seen late, neither had any effect. However, while the two drugs appeared to be equally effective to me, the patient thought ergotamine gave more prolonged relief, although it made her sick.

Headache started with pain in the left eye and then involved the entire head. Attacks varied from mild to very severe. The usual drugs were ineffective, as were the so-called antihistaminics. Epinephrine and ergotamine both helped. Ephedrine orally was useless.

The third case was that of a forty-two-year-old man. Migraine was present for about twenty years. He had a very nerve-racking job which upset him a great deal. He was also allergic to chocolate, anything containing vitamin B in the form of medication, and liver injections. These initiated migraine as well as nervous tension. The ordinary drugs gave no relief. Demerol, codeine and morphine by hypodermic administration gave temporary help until they wore off. They did not stop an attack. Ergotamine was ineffective orally or subcutaneously. Mild amelioration of the syndrome could be effected by epinephrine for short periods of one-half to one and one-half hours. It aborted light attacks. Doses of .05 c.c. were used.

Attacks started with pain over the right eye and then spread to the right posterior head and neck. In severe headaches the whole head became involved. Dizziness, nausea, vomiting, and visual disturbances ensued. The patient was seen in about twenty attacks of migraine. In severe ones neither epinephrine nor any other drugs were effective.

The fourth case was that of a twenty-eight-year-old man. He had migraine for about eight years. Nervous tension or sudden extremes of temperature would bring on an attack. This was characterized by hemicranial headache. At first these responded to aspirin and related compounds. Later they became more resistant, and sedatives were needed. Ergotamine was of no avail. Epinephrine in doses of .05 c.c., repeated if necessary, would stop an attack. He was seen twice.

The fifth patient was a small, highly neurotic woman of fifty-two years of age. Her condition was complicated by asthma and a multiplicity of food allergies. Economic pressure was severe. Migraine dated from the loss of her husband five years ago. Headaches were right-sided, being confined to the right temporal and occipital areas. Visual, equilibrium, and gastro-intestinal symptoms were present. Epinephrine in doses of .025 and .05 c.c. and ergotamine both alleviated the syndrome. The former was preferred because there were no side effects. The patient was seen twice.

The sixth patient was a twenty-five-year-old girl with a history of migraine of two years' duration. The patient had an explosive personality and a migraine which could be elicited by tension or eating of chocolate. Both ergotamine and epinephrine in small doses of 0.25 c.c. would stop the attacks. The headaches were moderately severe. She preferred ergotamine as she said the effects seemed to last longer. The patient was treated on three occasions.

The seventh case was that of a thirty-five-year-old woman who had the syndrome for seven years. She had a left hemicranial involvement. There was no history of allergy. She was seen only once. She had used ergotamine, which gave her the usual side effects. After being relieved by epinephrine in a dose of .05 c.c., she stated that she preferred this drug to ergotamine because she had no side effects from it.

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Progress in Allergy

DERMATOLOGIC ALLERGY

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In resuming authorship of the progress notes on dermatologic allergy, the present writers refer the reader to the excellent review by Epstein and Macaulay[24] on the more recent publications on dermatologic allergy and also to their own previous review[7] where an extended discussion was given on the general theory of allergy. In the previous review it will be found stated that adherence to the precepts of von Pirquet,[97] Schick and Sulzberger[89] still forms the most secure foundations for the concept of allergy. The newer knowledge of immunology, serology, biochemistry and biophysics of antigens, antibodies and antigen-antibody interaction has served to point up the sturdiness of the foundations laid down by them. The heuristic value of the original concept of allergy as acquired, specifically altered reactivity in the direction of either increased or decreased sensitivity is what made so many recent advances possible. Consequently, one must deprecate the latter-day looseness of equating allergy only with clinical hypersensitivity and dissociation of acquired immunity from it or of talking of allergy as something that always is based on a histamine mechanism. In fact, a good case can be made out to prove that all allergic transformations are beneficial *in intent;* and even if some allergic changes are harmful *in effect,* many more are life saving.

ON THE USE OF CERTAIN WORDS, TERMS AND PHRASES IN THE FIELD OF ALLERGY

One often reads articles or hears technical conversation in which a patient is referred to as "an allergic" or statements are made to the effect that "there is (or there is no . . .) past history of allergy" or "there is (or there is no . . .) history of allergy in the family." It would seem that the implications attaching to allergy from the above contexts are misleading. For one thing, it is suggested that allergic transformations are somehow always pathologic and harmful and that a person who acquires, or who is capable of developing, an allergic state is inherently a special sort of person, quite different from ordinary mortals in health or disease. In reality, the skin is an excellent indicator of the fact that no one can exist long in this world without quickly developing allergic states or responses to many things. For example, nearly everyone who gets vaccinated against smallpox or immunized against diphtheria and tetanus or injected with pertussis, influenza, cholera, yellow fever vaccine, et cetera, becomes allergized. Even without these artificial events, from the moment of birth, perhaps even in gestation, specifically acquired altered reactivities begin to develop against foods, microorganisms, inhalants, contactants, drugs, et cetera. So everybody has a past history or background of allergy in himself and family, and that makes everybody "an allergic."

This semantic confusion arises because so many of the clinical problems in the general field of allergy are of the category that has been aptly designated as *atopy.* Now, it is all right to refer to a human being as an atopic or to state that there is (or there is no . . .) history or background or family history of *atopy.* The atopic is indeed a bit of a person apart. About 10 to 30 per cent of the population is said to be of the atopic habitus and thus candidates for diseases associated with the atopic tendency. The other 70 to 90 per cent are apparently incapable of spontaneously developing atopic disabilities nor can the majority of the atopic states be induced in them artificially. All persons, however—atopics and non-atopics—are

capable of acquiring, in the course of natural events or by experimental means, any of the *other* varieties of allergic transformations, e.g., eczematous sensitizations, tuberculin-type sensitizations, drug sensitizations and eruptions and immunities based on stoichiometric neutralization of toxic antigens by specifically developed neutralizing antibodies.

Another rather objectionable use of the word "allergic" is when it is employed as an adjective to modify a material as in "non-allergic covering" or "hypoallergic nail polish." Obviously the word "allergenic" is intended. All of this may seem to be carping objection, but we find that the lay public as well as even some of the general medical public is confused by this misuse of words.

ALLERGIC ECZEMATOUS CONTACT-TYPE DERMATITIS

Eczematous sensitization is still a major dermatologic problem. Considerable strides have been made during the past years in elucidating the manner of induction and maintenance of this allergic state, the mediation of it by allergens and antibodies, the modification of it by hyposensitizing procedures and through "spontaneous" loss of sensitivity.

In the diagnosis and management of allergic eczematous contact-type dermatitis, it would not have occurred to most workers in this field that the patch test properly applied and interpreted is not of indubitable value. But it is Sutton's[91] thesis that the patch test is overrated and largely needless, as he finds it adequate in cases clinically diagnosed as dermatitis venenata to institute a rigid local quarantine of the affected area, permitting nothing but the patient's hands, water, air, petrolatum, cellulose and selected cotton coverings to approach it until improved (an optimistic two weeks) and then to practice gradual re-exposure to various contactants until the allergen culprit reveals itself by a clinical recurrence or exacerbation. This advocacy of a routine of elimination and re-exposure would have been a progressive recommendation about thirty years ago, before the easy, much more harmless and frequently definitive patch test routine was perfected. But as of modern times, it is a backward step to suggest that finding the specific cause in cases of eczematous sensitization is academic perfectionism. Suppose, for example, that it is found in a particular case that an eruption arises from the wearing of a particular fur coat or a certain pair of shoes or metal earrings. Would it be enough to say that this fur coat, that pair of shoes or these earrings are at fault and that with avoidance thereof the problem is ended? It is quite possible and even probable that it is merely the paraphenylenediamine of the rabbit dyed mink that is the allergen. Then obviously genuine mink can be worn, but all other materials containing paraphenylenediamine or treated with this material, be they hair dyes, furs, cotton or leather, are extremely likely to be harmful. In general, it should be the physician's objective to prove, if possible, the specific substance, i.e., often the simple chemical in a material, that is causative, because only then a whole class of contactants may be advised against prophylactically. Aside from the inadequacy of Sutton's routine in the practical management of allergic eczematous contact-type dermatitis, it is hard to imagine how further progress can be made in eczematous contact-type allergy by such incomplete investigation.

Complete and detailed studies have brought us newer knowledge on multiple epidermal sensitization on the basis of cross-sensitization between chemically or immunologically related substances. It has been long known that substances may be so related that while allergic sensitization may be induced by a solitary agent, the allergic state sometimes may be elicited by other compounds which are related to the original sensitizing substance. Cross-reactions between the oleoresins of ragweed and pyrethrum and between poison ivy, oak and sumac were early observations. The original work of Mayer[59] in 1928 and the recent investigations of Sidi,[81,82] Dobkevitch,[21,82] Meltzer,[62] Leider,[8] Mayer[8,60,61] and Baer[6,8,21] on substances which

contain an amino-group in the para position on the benzene ring bring the subject down, at least for this group of relatively simple chemicals, to more desirable levels of chemical and molecular structure, positional arrangement of radicles, et cetera. Thus Mayer's revelation of the formation of compounds of quinone structure, their allergenic activity resulting from the chemical transformation of paraphenylenediamine and the similar transformation of azodyes, and the subsequent demonstration of cross-reactions to other substances, on a chemically as yet unexplained basis by Sidi, Dobkevitch, Baer, Leider, and Meltzer, have opened up new possibilities of predicting and explaining hitherto mysterious persistence and exacerbation of eczematous episodes by overt or occult exposures to chemically or immunologically related substances.

The occurrence of an extremely wide spectrum of hypersensitivity to this group of substances in a patient with allergic eczematous dermatitis due to monoglycerol ester of para-aminobenzoic acid is described by Meltzer and Baer.[62] The patient reacted to many sulfonamides, local anesthetics, nitro compounds, azodyes, paraphenylenediamine and aniline. Despite the extent of the sensitization, it was still considered specific for compounds which contain an amino group in the para position on the benzene ring.

Laden and Wallace[43] studied eight cases of contact dermatitis of the hands due to local anesthetics, an occupational dermatosis in dentists. All cases were due to procaine or closely related compounds; para-aminobenzoic acid did not produce positive tests.

The fact that not all reactions ensuing after penicillin injections are due to penicillin itself is indicated by the case of Peck and Feldman[68] of a hand eruption in a physician due to the procaine in procaine penicillin. Cross-sensitization to certain other local anesthetics, sulfonamides and nitro compounds was present as in the cases of Sidi[81] and Meltzer and Baer.[62] That the eczematous sensitization to this type of compound can be made manifest by oral administration of these compounds was demonstrated by Sidi and Dobkevitch[82] with feeding of procaine and sulfonamides. The feeding caused eruptions, flareups of old sites of dermatitis and fever. This fits in with the results of feeding certified food azodyes in paraphenylenediamine-hypersensitive subjects in as yet unpublished experiments by the reviewers.

Another condition which furnishes an explanation of persistence and exacerbation of sensitization dermatitis is the contamination of inherently innocent materials by minute amounts of powerful sensitizers or the presence of them as residual traces in otherwise inert masses. Examples of these events are cases where cold creams, deodorants, and other innocent cosmetics became contaminated with nail polish or paraphenylenediamine, to which sensitivities existed, and then were incriminated as causes of the dermatitis (Leider and Furman[52]). The failure to realize that hand-borne allergens can be widely distributed to other materials permits chronicity of dermatitis to be established by continuous exposure to these contaminated materials despite elimination of the major source of allergen.

Whereas strict avoidance of discoverable allergenic causes is almost always perfectly satisfactory management of allergic eczematous contact-type dermatitis, some patients demand, and some situations would make desirable, a hyposensitization or modification of hypersensitivity by some routine like repeated exhibition of the allergen in graded doses on the skin.

To date we know of no study which shows reversal of epidermal sensitivity to original insensitivity by a feasible and repeatable technique which is effective in 100 per cent of cases. It is probable that the levels of sensitivity in eczematous sensitivity fluctuate spontaneously and sometimes fall to zero after long avoidance of previously exciting allergens and particularly often in the aged. The lesser incidence of poison ivy sensitivity, for example, in older age groups compared to that in youth or young adulthood may reflect this trend. The phenomenon of "hardening" is an-

other circumstance which perhaps is clinical specific hyposensitization, but it is usually only a temporary immunologic reversal, judging by the frequently observed reappearance of sensitivity after an adequate period of avoidance and then re-exposure. In the study of Witten and Shair[103] on the effect on the level of sensitivity of repeated application of simple chemical allergens by patch test, no lessening of sensitivity was observed. No consistent or persistent change in degree of sensitivity could be demonstrated. If anything, the level of sensitivity seemed to rise after repeated application of the allergen. These findings even contradict the clinical observation of hardening—at least with respect to the substances they worked with, the quantities used, time intervals of application, et cetera.

The most hopeful method of favorably modifying epidermal sensitization in some cases is by feeding or parenteral injection of corresponding allergen. In cases of poison ivy, ragweed pollen, grass pollen and pyrethrum sensitization there seems to have been some measure of success. Ingraham[38] and Slater et al[87] have reported clinical abatement and decrease of sensitivity, confirming earlier studies, particularly those of Shelmire.[37] It is difficult to explain the mechanism of this improvement. Knowing nothing of antibody action in eczematous sensitivity in man, one can but be content for the time being with the satisfactory practical result. In this connection studies by Chase[16] show that in the guinea pig prefeeding with a powerful eczematogenic chemical (picryl chloride) tended to prevent or at least lessen the intensity of subsequent induction of "epidermal" sensitization, but feeding after induction of sensitization did not influence established sensitivity. This finding is in direct contradiction with what apparently happens in the oral and parenteral treatment of plant and pollen contact dermatitis in man.

Many papers have appeared on the value of antihistaminics in allergic eczematous contact-type dermatitis by both topical and oral administration. Mayer[61] conducted a laboratory study on animals and reported results which were interpreted to show favorable effects of Pyribenzamine on experimentally induced contact dermatitis, both from primary irritants and from allergens. However, the doses of antihistaminics used were much larger than those considered permissible in man. Others have reported clinical and statistical studies with variable claims of benefit. The sum total of effectiveness described in all these reports does not impress us. It appears possible that cases of epidermal sensitization as are attended by some degree of urticarial edema have some beneficial effect from antihistaminic therapy. Our own experience is that the effect of antihistaminics in contact dermatitis is purely antipruritic. What impresses us is the increasing number of case reports of eczematous sensitization from "antihistaminics" (see under drug eruptions).

Allergic eczematous contact-type dermatitis is one of the most obvious of allergic transformations. It fulfills every clinical criterion of acquired, specifically altered reactivity. But, at the same time, it is one allergic condition in which the demonstration of antibodies and antigen-antibody interaction has been least possible both *in vitro* and *in vivo*. In the allergy of infection (to be discussed more fully below), in the atopic and anaphylactic varieties of allergic change, there are several methods of demonstrating antibodies and antigen-antibody interaction. In atopy, in anaphylaxis and in the case of the neutralizing antibodies involved in immune states, the presence and sometimes the production of antibodies can be shown by repeatable techniques. They frequently can be isolated and titrated *in vitro*. They can be demonstrated *in vivo* by all sorts of procedures like the Prausnitz-Kustner reaction and modifications of it. In allergic processes due to infectious microorganisms antibodies may be shown like the pro- and anti-cutins of tuberculosis, the reagin and immobilizing antibody (Nelson[65]) in syphilis, et cetera. But in eczematous allergic sensitization much less evidence can be produced. In the older literature modifications of the Prausnitz-Kustner experiment have sometimes been reported to have demonstrated antibodies in cases of eczematous sensitization (Biberstein[12]). For example,

with the Koenigstein-Urbach method, several experimenters have claimed success in demonstrating something in the blister fluid from areas of allergic dermatitis which can passively transfer eczematous sensitization. The present authors[51] have tried this procedure and have not been able to reproduce the results claimed by others. Again the work of Landsteiner and Chase[45] and others must be cited as evidence that the carriers and possibly also the producers of antibodies both in eczematous sensitization to simple chemicals and in tuberculin-type sensitivity are certain elements of the leukocytic system, i.e., the monocytes, lymphocytes and plasma cells. Their experiments on the passive transfer of such sensitivities by means of washed cells from peritoneal exudates rich in leukocytes and their[44,46] and Rostenberg's[78] experiments on the route of dissemination of epidermal sensitization place the locus operandi in the reticuloendothelial system. A pertinent study in this connection is that of Nexmand,[66] who examined the cellular content of bullae produced by primary irritants and of those from true allergic dermatitis. He found that the latter had a high lymphocyte count whereas the former contained predominantly polymorphonuclear leukocytes. It is possible that blister fluid with properly high lymphocyte count may be effective material for successful accomplishment of transfer by the Koenigstein-Urbach technique. The bridge between all these studies in animals to sensitization in human beings has been furnished by the successful passive transfer of tuberculin sensitivity accomplished with viable leukocytes by Lawrence.[47] His source of white cells was the blood stream and 50 c.c. of blood yielded a sufficient amount of cells to effect transferability. It remains to be seen if a similar procedure will be successful in the transfer of eczematous sensitization.

Kalkoff[40] tried, in the guinea pig, to inhibit spreading of eczematous sensitization from the site of application of the sensitizing agent. Similar to previous work by Landsteiner and Chase, this was done by making a skin island, by excising a band of surrounding skin to a considerable depth, but Kalkoff was unable to prevent the spreading.

Crepea and Cooke[18] succeeded in passively transferring sensitization to poison ivy in guinea pigs by means of washed splenic cells in sixteen of nineteen animals and by means of sera in seven of fifteen instances. While the transfer with splenic cells fits in with previous work by Landsteiner and Chase,[45] the transfer by means of sera is a novel phenomenon, unless the sera were not entirely cell free.

Hollstrom[36] did experiments where patients, subsequent to sensitization to 2-4 dinitro-chlorbenzene, were inoculated with tertian malaria. Thirteen of fifteen such patients did not react to the substance three weeks later. In the not-fever-treated control group, thirteen of fifteen patients showed positive reactions to 2-4 dinitrochlorbenzene. These experiments are a significant contribution to our knowledge regarding the factors producing changes and fluctuations in eczematous allergies. The use of the term "epidermal" allergy by Hollstrom is not advisable. In view of the fact that it is still unknown where all the various phases of eczematous sensitization take place, it is better to refer to "eczematous allergy." Another interesting experiment in allergic sensitization was done by Haxthausen,[32] who tested whether allergic eczematous reaction in a piece of skin interferred with its vitality. Using a modified pinch graft technique, he found no evidence of impairment in vitality of the tissue.

In the histopathogenesis of allergic eczematous contact-type dermatitis, the inflammatory dynamics have long been a matter of study and speculation. Since the epidermis is an avascular structure, it is a question of how and why fluid and cells reach the area in sufficient volume to produce spongiosis, vesiculation and bulla formation plus exocytosis of leukocytes. Polak and Mom[71] studied the problem by special histologic techniques and confirmed the thesis of Civatte that lysis and death of malpighian cells by the allergic process is the quintessential lesion. Following upon this there is variable influx of fluid and cells as a secondary effect from the

papillary vessels of the underlying true skin. This paper is illustrated by beautiful and convincing high-power photomicrographs which show the stages of the basic and initial epidermal damage. This visualization of the early allergic events in the shock organ is important but still not as important as the biochemistry of the phenomenon would be. However, it may be a forerunner of such humoral elucidation and may be important to such problems as the site of antibody formation, lodgment and interaction with allergen.

Werz[101] observed dermatitis due to quinine in a quinine plant in twenty-two workers, i.e., in 10 per cent of the workers. The high incidence was thought due to the employment of a large number of unselected workers after the war.

Higgins and Kindel[33] saw a case of exfoliative dermatitis due to a DDT spray. Patch tests were positive to DDT and two of thirteen chemically related agents. DDT sensitivity was no longer demonstrable two months after healing of the eruption. This is a rather unusual occurrence, as allergic eczematous contact sensitization usually persists for a long period of time. However, allergic sensitizations to certain substances, e.g., penicillin, perhaps tend to become lost more often than sensitizations to most substances.

A case of eczematous dermatitis due to Intracaine is reported by Rein and Kanof.[76]

An apparently allergic eczematous reaction caused by aged silver nitrate solution occurred in a patient of Gaul and Underwood, [27] whereas fresh solutions caused no reaction.

Eczema around the waistline and neck occurs in men working in young plantations due to a lichen, Parmelia Caperata, which grows on the older trees, according to Tenchio.[93] Patch tests with lichen material were positive on sweating skin.

Skinner[86] recorded a case of allergic eczematous dermatitis due to phenolphthalein. While this agent is an unlikely one to be contacted externally, it is of interest to find it capable of establishing still another type of allergic response in addition to others it is well known for, such as "fixed" eruptions and urticaria. Also, it is another illustration that every simple chemical must be suspect of ability to induce eczematous allergic states. This refers even to chemical elements, as for instance, the case of Robinson and Bereston[77] in which eczematous dermatitis was traced to mercury in amalgam dental fillings.

Seventy-seven cases of dermatitis due to green summer pascal celery were studied by Wiswell et al.[102] There was some evidence that immunity can be developed. Injections of diluted celery oil in two highly sensitive workers were successful in producing protection.

Another series was reported by Arnold[3] where dermatitis due to the light sensitizing effect of parsnips occurred in a military camp in 1940. Patch tests with parsnip material were negative. This type of sensitivity is not based on an allergic mechanism and must be differentiated from allergic contact dermatitis as it is based on a nonallergic photosensitizing effect.

There are three types of adhesive tape irritation, according to Peck et al[69]: (1) a fleeting reaction, due to the trauma of tape removal, (2) a reaction due to specific allergic sensitization to one or more components of the tape—this reaction is rare—and (3) a reaction due to changes in pH and in the bacterial flora under the tape—this is the most common reaction due to adhesive tape. The addition to the adhesive mass of the tape of fatty acid salts, such as zinc caprylate and zinc propionate, reduces the bacterial flora and the degree of change in pH under the tape. Such tape, according to Peck et al, also produces much less skin irritation. However, Gaul and Underwood[26] failed to find any difference in irritancy of ordinary adhesive tape and tape containing fatty acid salts.

PROGRESS IN ALLERGY

ATOPIC DERMATITIS

No fundamental contributions have appeared in the past year on this important and not yet well understood condition. There have been a number of articles on various practical approaches. Particularly the one by Glaser[28] is valuable for new readers in the subject and those who want to bring themselves up to date. In the past, and still to a considerable extent today, articles on atopic dermatitis did not convey the great difficulties that exist in the management of very severe examples of atopic dermatitis. A realistic, even if highly discouraging, awareness of this situation can be found in an article by Hill.[34] This observer of long experience opens his paper with a statement to the effect that the longer he deals with infantile eczema, the less sure he is of what he is dealing with and of how to deal with it. Like a great many others, particularly dermatologists, he has departed from initial enthusiasm for the value of intracutaneous testing with protein allergens and management by elimination of substances that yield positive reactions. He is now at the point of asserting that only the exceptional case is benefited by such a course. For the rest, versatile management of each episode, largely by varied topical medicaments, is the best that can be done. In contrast, Tuft[96] still believes that there is great value in skin testing, particularly with inhalants in the older age group, and in desensitization with incriminated substances, most frequently dust. Tuft suggests that the best results can be obtained by combination of dermatologic, topical and systemic management plus a thorough work-up and treatment from the viewpoint of allergy.

In this connection it is worthwhile to consider the paper by Narins,[63] who called attention to the unreliability of scratch tests in testing for immediate wheal responses in atopic dermatitis. While intracutaneous tests produce repeatable results, scratch tests, even when done by the same person, with the same technique and in the same sites, produce completely unpredictable results.

Nexmand[66] published a detailed study on atopic dermatitis: 62.5 per cent of twenty-four patients who were worse during the summer gave positive skin tests to pollen extracts, often associated with a flareup of the eruption and hay fever. Only 17.8 per cent of patients who did not get worse during the summer gave positive pollen tests, and only one of these had hay fever. Nexmand states that positive skin tests with food and inhalant allergens are rare in the one-to five-year age group Positive skin tests with inhalants are much more frequent than those with foods in the age group over five.

A new approach to the atopic dermatitis problem, which has found insufficient attention on the part of allergists and dermatologists is the work by Sulzberger et al[90] on the possible importance of the "sweat retention syndrome" in atopic dermatitis. These workers found failure of sweating and cutaneous lesions due to plugging of the sweat gland openings, similar to prickly heat, in the histologic sections of some atopic dermatitis patients. This fits in with the well known facts that (1) some atopic dermatitis patients tend to get much more itchy upon physical exercise and exposure to heat, (2) many atopic dermatitis patients show a fine papular eruption over the trunk (plugged sweat pores?) and (3) the marked improvement of atopic dermatitis patients in *dry* hot climates where the evaporation of sweat is not hindered by high atmospheric humidity. The full clinical evaluation of these findings by Sulzberger et al still awaits further study.

A refreshing approach to the problem of atopic dermatitis in recent years has been that of Simon[83,84,85] with his work on allergens in human dander, in skin generally, in scales from some dermatoses and in comedones. These allergens give reactions in some subjects with atopic dermatitis and no reactions in normal controls. Patch tests with human dander (50 per cent in petrolatum by volume of the crude material as obtained from combings) give eczematous responses in atopic dermatitis patients about half the time and very few such reactions in normals. We ourselves have been able to confirm this in a small series of cases. Intracutaneous tests with extracts from

dander, apparently normal skin scrapings, scales and sebaceous concretions give immediate urticarial reactions in Simon's experience. The clinical significance of the patch test and intracutaneous test reactions to these allergens is as yet unknown. That there may be some clinical importance to the dander allergen could be suspected on the basis of the fact that for many years it has been a cardinal rule of dermatologic treatment of atopic dermatitis that scaling and seborrhea of the scalp must be treated in all cases where it is present. In some ways it would be satisfying to explain and excuse one's helplessness with some cases of atopic dermatitis by believing that such patients are sensitive to their very selves, and so being, how can one be effective in such a hopeless situation? We think that Simon's interesting findings also are another confirmation of the well-known capacity of atopics to acquire multiple immediate wheal reactions to allergens similar to the reactivity to egg, wheat, milk, fish, et cetera.

Bartlett[9] cites a case in which he established by skin test, passive transfer tests and by tests of avoidance and exposure that sensitivity to a specific human scalp dander was present and the sole cause of an allergic dermatitis (atopic dermatitis?). There was no sensitivity to stock scalp dander or to the body dander of the person whose scalp dander elicited the dermatitis.

Charpy[15] administered unsaturated fatty acids, pyridoxine and intestinal vaccines (per os) to 250 cases of infantile eczema, with improvement in 70 per cent. In view of the combination with pyridoxine and vaccine, it is difficult to draw conclusions as to the efficacy of the fatty acid therapy itself. Azerad and Grupper[5] also gave unsaturated fatty acid to seven patients with infantile eczema, in all of whom recovery ensued. Our own experience with unsaturated fatty acid treatment of infantile eczema and atopic dermatitis in children, adolescents and adults has thus far not aroused great enthusiasm in us for this sort of treatment.

DRUG ERUPTIONS

It is striking how many allergic drug eruptions are aroused by such innocent and relatively nontoxic drugs as the antibiotics and so-called antihistaminics. For example, contrary to a widespread belief, severe and potentially fatal, although extremely rare, erythrodermas can be caused by penicillin. Andrini[4] relates a case of erythroderma due to penicillin. Specific therapy and at the same time desensitization is said to have been carried out by continued administration of very small doses of penicillin. Another case of exfoliative erythroderma after penicillin, and this one with fatal outcome, was recorded by Rabinovitch and Snitkoff.[74] However, their evidence that death was due to the penicillin is not conclusive.

Goldman and Farrington[29] observed two cases of stomatitis and glossitis after oral administration of penicillin tablets. Isled and Karabadjakian[39] claim that they demonstrated a common antigen in penicillium notatum and achorion quinckeanum. The various reactions which can be caused by penicillin are summarized by Black et al[14] as follows: (1) urticarial, (2) vesiculo-bullous, (3) contact dermatitis, (4) serum sickness, (5) stomatitis and pharyngitis, (6) ocular reactions, (7) asthma, (8) angioneurotic edema, (9) purpura, (10) sterile abscesses, (11) headache, fever, vomiting, and (12) questionable reactions as erythema nodosum.

Peck et al[70] conclude from their studies that in penicillin sensitization the test for delayed tuberculin-type reaction offers a reliable index of sensitivity but that the patch test and test for urticarial response are unreliable. This is in contradiction to Farrington and Tamura[25] who utilize 0.1 c.c. of 2.5 to 2,000 units of crystalline penicillin G or K per c.c. in saline as an indicator of urticarial penicillin hypersensitivity.

Touraine and Pichon[95] observed twenty-three cases of streptomycin eruptions among hospital personnel. The problem of sensitization to various antibiotics has also been studied. Berke and Obermayer[10] patch tested a group of fifty-five nurses

and obtained 39 per cent reactions to streptomycin, 39 per cent to procaine, 25 per cent to penicillin and 4 per cent to tyrothricin. Another case of rare tyrothricin sensitivity is reported by Goldman, Feldman and Altemeyer.[30] The sensitivity crossed over or at least also was present to bacitracin and other antibiotics.

The great number of allergic eruptions due to contact with antihistaminics and the less numerous, but still very important, eruptions due to the ingestion or injection of these "anti-allergic" or "antihistaminic" drugs may have its humorous aspects for those interested in the theoretical background of these substances. However, the reviewers are quite certain that these eruptions and the itching associated with them are not considered jokes by the so afflicted patients. While the application of most "antihistaminic" ointments produces a low incidence of eczematous allergic reactions, a high incidence has been reported for Thephorin ointment by Ellis and Bundick[23] and Howell.[37] Other observers, including Laymon and Schmid,[48,49] report no unusually severe reactions from Thephorin ointment. The experience of the reviewers suggests that Thephorin ointment produces more allergic sensitizations than is allowable for a therapeutic agent with purely antipruritic effects but that the incidence is not as high as the 28 per cent "clinical reactions" in Ellis' series. In the reviewers' opinion, antihistaminic ointments should be used with circumspection and preferably not in cases of allergic eczematous contact-type dermatitis because these latter cases have, as a group, a greater than normal capacity to undergo eczematous sensitization.

London and Moody[58] record a case of urticaria which was very obviously due to Pyribenzamine from the circumstance that whealing occurred within an hour of exhibition of the drug upon two occasions. Notably, the first occasion of the eruption was, as far as can be told, the very first encounter with the agent. Unless the history is faulty, this would suggest that this urticaria was not on an allergic basis inasmucli as there was no incubation period of sensitization. However, it is more likely that there was a pre-existing sensitization due to exposure to a chemically related agent which was not discoverable in the history.

Rattner and Graffin[75] report a case of extensive dermatitis proved to be due to orally administered Pyribenzamine by trials of elimination and re-exposure. The case was complicated by a history of previous administration of gold parenterally for arthritis. The Pyribenzamine was given for a pruritic dermatitis of the ears, the nature of which was not specified. After Pyribenzamine was found to be the source of the trouble, Benadryl was administered without event, which is not remarkable, considering that the substances are not chemically related.

One of us (RLB) together with M. Yanowitz has seen a case of urticaria due to Chlor-Trimeton. Bellach[11] observed many of the characteristic immunologic phenomena in a case of sulfapyridine hypersensitivity. A case of "fixed" eruption due to sulfadiazine has been studied by Meltzer. Sulfamerazine also elicited the reaction but not para-aminobenzoic acid.

Tolmach and Frank[94] described the first case on record of a "fixed" drug eruption due to bromides. Aguilera and Cadinanos[1] report a case of tuberous iododerma on the face of a breast-fed seven-month-old infant due to transmission of iodine by maternal milk. The mother had been receiving two injections of an iodopeptone compound.

A case of urticaria due to mercupurin was investigated by Gottlieb.[31] Scratch-patch test produced within two hours an urticarial eruption (not locally at the test site) and a papular erythematous eruption at the test site after twenty-four hours. Salyrgan-Theophylline produced a similar reaction in a scratch-patch test. Dobkevitch and Sidi[22] noted a case of eczema of the face due to a collyrium of atropine sulfate.

URTICARIA

As for atopic dermatitis, no new or fundamental studies have appeared on urticaria. This subject, together with atopic dermatitis, and to a less extent the rest of the field of allergy, suffers more year by year from indiscriminate psychosomatic explanation.

The only tangible advances have been in the further development of the heterogeneous group of compounds which have therapeutic kinship in their suppressing effect on the mechanism of whealing. There has been less emphasis lately on straight histamine antagonism as an explanation of their action, although the attractiveness of the histamine theory as the basis of some forms of allergic hypersensitivity still appears to be great for some workers.

Despite the sometimes miraculous effect of the anti-urticarial agents, no deep satisfaction derives from them in definitive management of urticaria similar to many cases of allergic rhinitis, asthma, et cetera. It is true that they effectively carry over the patient in acute, self-limited urticaria; and in some cases of chronic urticaria they reasonably control whealing and/or itching so long as they are taken constantly. But rarely is the patient, or the medical advisor, content with such continuous medication, even though usually harmless. One is still left with the problem of etiologic resolution.

What is still urgently required are studies on large series of cases of urticaria with statistical and other data on what percentage is ultimately proved to be allergic, what fraction nonallergic. And of those that can be proved allergic, how many can be shown to be due to (1) foods, (2) drugs, (3) inhalants, (4) bacterial allergens, (5) physical agents, (6) autochthonous materials and other agents.

Wadulla[98] saw a case of urticarial eruptions on both legs due to ultra-short wave therapy on the right leg. The eruption on the left leg was explained on the basis of a reflex mechanism. In Polano's[72] case sun exposure produced wheals, fall in blood pressure, shock and collapse. A similar condition was present in other members of the family.

ERUPTIONS DUE TO INSECTS AND PARASITES

Many, if not all, cases of papular urticaria are actually due to insect bites. This has been shown by Shaffer, Spencer, and Blank.[80] Many cases of papular urticaria are cured by use of a lotion containing 5 per cent DDT; and patients with papular urticaria give a much higher incidence of positive skin tests to extracts of fleas and bedbugs than groups of control patients without papular urticaria.

Carpet beetles can cause eruptions of papulo-vesicular and urticarial character, as shown by a case of Cormia and Lewis.[17] Larvae hairs produced a local reaction and a distant cutaneous response.

Eruptions due to contact with moths were seen by Hill et al[35] in three members of a tanker crew. The lesions were papulo-vesicular, erythematopapular and urticarial in character. Patch tests were positive.

Schoch[79] states that of 100 unselected patients tested with ascaris allergen 55 per cent showed positive immediate wheal responses. Desensitization was attempted in eight patients, with some improvement in their dermatoses. Schoch's figures indicate that the skin test with ascaris antigen, at least in his group of patients, is not of diagnostic value. This comes as no great surprise, as sensitization to one helminthic parasite is known to bring on skin sensitization to the extracts of other helminths as well.

THE ALLERGY OF INFECTION

In the recent past there has been a rekindled interest in the allergy of infection,[92] particularly as represented by the disease processes of syphilis and tuberculosis. The concept of the "id" and the explanation of some effects of infectious diseases by autosensitization to injured body-own tissue have received considerable attention.

In the case of syphilis, even the attainment of apparently successful and permanent cure with penicillin has not made theoretical considerations seem superfluous as shown by the new work of Nelson and others on spirochete culture, immobilizing antibodies, new serologic techniques and related phenomena. But especially in the case of tuberculosis and allied diseases, where no entirely satisfactory antibiotic therapy is available, the allergic states engendered by them, the clinical expressions of those allergic states and finally the meaning of those allergic states in terms of protection (immunity) or harmfulness (disease) are ever timely subjects for study.

About ten years ago, Kveim[41] set into motion a great deal of new work and speculation on the relation between tuberculosis and sarcoidosis by describing a novel skin test for sarcoidosis. The test material is an "antigen" processed (in a manner similar to Frei antigen) from histologically proven human sarcoid tissue. A positive reaction to the intracutaneous deposit of this material consists of a delayed papular to ulcerous lesion (weeks to months after injection) which upon microscopic examination shows sarcoid structures. Such positive reactions are said to occur only in patients suffering from sarcoidosis in one of its many forms (Boeck's disease, Schaumann's disease, Jungling's disease, Heerfordt's disease, et cetera). Kveim interpreted his findings as proving that sarcoidosis is a disease entity *sui generis*, i.e., of unknown cause but definitely not of tubercle bacillus causation. For some fifty years prior, debate had raged on whether sarcoidosis is a disease *sui generis* or whether it is merely a reaction form, i.e., whether it is an expression of various infectious diseases, particularly tuberculosis. The likelihood that at least many cases of sarcoidosis are in some way connected with tuberculous infection had been established by the positive anergy to tuberculin (see below) which is demonstrable in many cases of sarcoidosis. The Kveim test has by no means settled this issue; in fact, it has given new impetus to experiment and argument. The correctness of Kveim's observations concerning the skin test has been amply confirmed by many observers, namely, abroad by Danbolt,[20] Lomholt[57] and Putkonen[73] and in this country by Nelson[64] and Leider.[50] However, there is no agreement as to the relative specificity of this test which is now generally called "Kveim test." The interpretation of the test by the above workers is also still a matter of dispute among them, as is the background question of the relationship between sarcoidosis and tuberculosis.

In a re-examination of the subject, Leider[50] found that at least two observers before Kveim showed that characteristic reactions could be obtained in sarcoidosis with tubercle bacilli. Lemming[55,56] accomplished this with BCG vaccine, and Warfvinge[99,100] did the same with living virulent human tubercle bacilli. The reactions they obtained were clinically and histologically compatible with natural sarcoid. Following all of these leads, Leider and Sulzberger[54] and Leider and Hyman[53] undertook to study the clinical, immunologic and histologic responses of the skin to BCG vaccination in various categories of tuberculin sensitivity in man. Certain theoretical considerations suggested that several different types of clinical, immunologic and histologic responses would occur, depending on the nature of the tuberculin reactivity present, and in particular that the peculiar lack of tuberculin reactivity in many cases of sarcoidosis would produce characteristic and distinctive results. The gist of this work may be summarized as follows: There are four distinguishable conditions of tuberculin reactivity, namely:

1. Native or original anergy (no reaction, even to concentrated tuberculin) which is the nonreactive status with respect to tuberculin that exists in man and many lower animals prior to adequate exposure to the tubercle bacillus.

2. Normergic and hyperergic reactivity to tuberculin (reaction to tuberculin up to dilutions of 1:10,000) which are the common sensitive states that come into being after adequate exposure to the tubercle bacillus. These reactivities are allergic transformations.

3. Positive anergy or relative hypoergy (no reaction to tuberculin 1:100 up to undiluted tuberculin) which is comparative insensitivity to tuberculin that sometimes ensues after infection with, or adequate exposure to, the tubercle bacillus. Positive anergy is different in quality from native or original anergy in that it is not a return to aboriginal insensitivity but rather is progression into another acquired, specifically altered capacity to react to the tubercle bacillus and/or its products. In other words, positive anergy is another allergic transformation but one in the direction of lesser reactivity and possibly after a previous condition of normergic or hyperergic reactivity.

4. Negative, nonspecific or absolute anergy which is transient nonreactivity to tuberculin that is induced by certain intercurrent febrile diseases and cachectic or debilitating states. It is not a true immunologic status but rather a passing expression of interference with established immunologic phenomena by incidental and repressive factors. In the condition of nonspecific anergy, reactivity to other tuberculin-type allergens, to wit, trichophytin, Frei material, et cetera, is also abolished or suppressed if such reactivity was previously existent. In short, established reactivity to tuberculin-type allergens continues to exist in potential during the condition of nonspecific anergy and reasserts itself if and when the repressive factors disappear.

In addition to these four forms of reactivity to tuberculin previously published, there must be considered a fifth form which occurs in the aged. In many aged persons tuberculin sensitivity is absent despite the fact that, at least in some of them, it had presumably been present at a previous time. This type of anergy in the aged has not yet been adequately studied from an immunologic viewpoint, and because of this it will be left out from further discussion in the present review. Individuals exhibiting any one of the first three categories of tuberculin reactivity respond clinically, immunologically and histologically to BCG vaccination in the following manners:

1. A subject who is natively or originally anergic to tuberculin responds to BCG vaccination with the first part of Koch's fundamental experiment, i.e., with an incubation period of some two weeks and then with an overt reaction of erythema through papulovesiculation, pustulation and ulceration to healing by scar in two to three months. Demonstrable tuberculin sensitivity comes into being at about the expiration of the incubation period. Microscopically the reaction is marked by banal polymorphonuclear inflammation in all the early stages of the evolving lesion and eventual appearance of tuberculoid structures toward the very end of it.

2. A subject who is already normergic or hyperergic to tuberculin responds to BCG vaccination with the second part of Koch's fundamental experiment, i.e., within a reaction time of twenty-four to forty-eight hours and then with an accelerated course of erythema, ulceration and scar-healing in some two to six weeks. Tuberculin sensitivity remains usually unchanged by merely one such vaccination. The histology of this reaction is in an early brief stage a banal inflammation and then rapid appearance of tuberculoid structures in later stages.

3. A subject who is relatively hypoergic or positively anergic, i.e., who is insensitive to tuberculin in the specifically acquired manner, responds to BCG vaccination with a papule that begins to become perceptible in about one week and then tends to last indefinitely as a torpid, non-caseating papule or as a slowly growing sarcoid-like plaque. Relative tuberculin insensitivity is usually not influenced by a single BCG vaccination. The histology of this reaction shows essentially and predominantly tuberculoid structures. The process is productive, proliferative and infiltrative with epithelioid cells.

The conclusions drawn by Leider, Sulzberger and Hyman from these studies are as follows:

1. The clinical courses of the responses of the skin to BCG vaccination in various categories of tuberculin sensitivity are characteristic and distinct.

2. The immunologic change from native or original anergy to normergic or hyperergic reactivity to tuberculin is particularly sharp and repeatedly demonstrable in proper subjects. The persistence of established reactivity and of established positive anergy to tuberculin are also repeatedly demonstrable phenomena.

3. The histologic pictures of the reactions to BCG vaccinations of the various categories of tuberculin sensitivity are not as finely distinctive as the clinical and immunologic events. Nevertheless, there is in these reactions a general trend of histologic progression from intense banal inflammation in the earliest tissue response to the tubercle bacillus in the natively anergic subject, followed by fairly classical tubercle formation in established hyperergic and normergic (tuberculin-positive) subjects and eventually to sarcoid-like pictures in subjects who become positive anergic.

Bjørnstad[13] and Danbolt,[19] whose experimental findings virtually duplicated the ones listed above in nearly every respect, arrived at entirely different conclusions. It appears possible now that all the results can eventually be reconciled and welded into a unitary theory of allergic transformation in the diseases marked by granulomatous processes.

Another important aspect of the allergy of infection, as it applies to dermatology, is the concept of "bacterids." It may be useful to examine for a moment what precisely is meant by the suffix "id." First, if we may be permitted another pedantic digression, it can be pointed out that the ending is a contraction of the Greek "ides" and has the force or meaning of "family relationship." In a proper name it means "son of" as in Christophorides (son of the Christ bearer) and is equivalent to O', Fitz,-son,-sen,-off,-witz, et cetera. Thus in words of general and not particularly technical context it carries the simple meaning of class relationship as in spermatid, fluid and liquid. The same applies to uses like leukemid, carcinomatid, et cetera. In uses in connection with certain infectious processes taking place in the skin the term has acquired connotations of allergy; thus Sulzberger defines an "id" as a secondary manifestation appearing in allergic tissue and produced by the microorganism and/or its products emanating from a remote focus.

In bacterid, the narrowed meaning here applies to eczematous and other lesions that result as a secondary manifestation appearing in allergic tissue and produced by ordinarily pyogenic organisms, particularly staphylococci and streptococci and/or their products emanating from a remote focus. Andrews[2] and Epstein have written extensively on the occurrence of this type of event in recent years. Proof usually consists in demonstrating the presence of microorganisms on culture in sites that have reputations as foci of infection and the clinical disappearance or remission of the eruption upon eradication of the focus of infection or upon specific desensitization to the particular microorganism. Such circumstantial evidence seems often convincing but not always, especially when the number of cases is small or when clinical improvement is only partial or not dramatic. Moreover, the question always remains unanswered whether the focus of infection was the cause of the eruption or was merely a contributory factor. However, Storck[88] reports experiments and skin tests to support the thesis that certain eczematous processes are the result of specific sensitization to products of bacterial pathogens. Implicated organisms in their order of frequency were found to be staphylococcus aureus, streptococcus hemolyticus and the colon bacillus. The significance of his findings is lessened by the fact that a high percentage of reactions was produced also in patients with normal non-eczematous skin. But Storck points out that the number of microorganisms present on the skin is much greater in some eczematous lesions than on normal skin. Particularly in acute exudative seborrheic dermatitis, coin-shaped mycosiform eczema and in eczematized neurodermatitis is the bacterial count quite high. It certainly appears possible that the eczematous sensitivity to the microorganisms could be a primary and perhaps more often a secondary factor in the production and maintenance of some eczematous lesions. This is especially true because a clinical parallelism can

be drawn between the classical allergic eczematous dermatitis from simple chemicals and such infectious processes as fungous infections. For example, the clinical picture in dermatophytosis is often predominantly epidermal, and as Sulzberger[89] has pointed out many years ago, the evolution and progression of superficial fungous infections sometimes appears as if they were based on sensitization effects similar to those caused by inanimate, simple chemical agents.

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962 Park Avenue (Dr. Baer)
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EPINEPHRINE IN THE TREATMENT OF MIGRAINE

(Continued from Page 127)

The eighth patient was a thirty-two-year-old man who had migraine for three years. Excessive amounts of wheat or chocolate could bring on an attack. He suffered from hemicranial syndrome. He was seen in one attack which was relieved by epinephrine in two doses of .05 c.c. Ergotamine had never helped either hypodermically or orally.

The ninth and tenth patients were supposed to have had migraine for three and five years, respectively. They had not responded to ergotamine and failed to respond to epinephrine also. The history was suggestive of migraine, but after a physical workup we found the patients to both be suffering from sinusitis. They had penicillin-sensitive organisms and responded to treatment. These cases illustrate the fact that one must be very careful about making the diagnosis of migraine and not accept too credulously previous diagnoses.

SUMMARY

Eight migraine patients had relief from small doses of epinephrine. In six of these the drug was considered more satisfactory than ergotamine. In the strength of dosage employed, no side effects were noted. If one accepts the concept of vasodilation as the pathologic physiology of the cranial vessels in migraine headaches, then epinephrine in small dosages is worthy of trial.

IN MEMORIAM

WILLIAM BYRON BLACK

WILLIAM BYRON BLACK, 57, A.B., B.S., M.D., was born at Windsor, Missouri. He received his high school and college education at Lamar, graduating from the Lamar College in 1914. He graduated from the University of Kansas Medical School in 1922, and his postgraduate studies were numerous. He taught at the Kansas City Municipal Hospital Department of Otolaryngology for nine years, and at the University of Kansas Hospital Clinical Department of Ophthalmology for eight years. At the time of his death he was teaching at the Kansas City Municipal Hospital and Menorah Hospital Ear, Nose, Throat Cancer Clinics. He was attending surgeon at the Kansas City Municipal Hospital, E.N.T. Charity Service, Menorah Hospital; and in the Ophthalmological Department, Kansas University, 1923-1931. He was a member of the Jackson County Medical Society and the Missouri State Medical Association. He was a member of the Menorah, Saint Joseph, Kansas City Municipal and Wesley Hospitals, and St. Vincent's hospital staffs. Doctor Black was past president, secretary, and treasurer of the Kansas City Southwest Clinical Society. He was a Fellow of the American Academy of Ophthalmology and Otolaryngology, American Medical Association, American College of Surgeons, American Triological Society, American Society of Ophthalmologic and Otolaryngologic Allergy, Diplomate American Board of Otolaryngology, and also a Fellow of the American Association for Advancement of Science. Doctor Black contributed a number of articles to important medical journals.

The passing of Doctor Black is a great loss to medicine. He was an inveterate worker and one of the most capable in his specialty. He practiced Ophthalmology as well as Otolaryngology. He attended practically every special graduate course offered in this country, consequently was adequately trained in allergy, bronchoscopy, plastic surgery, and fenestration surgery. He was one of the founders of the Kansas City Anatomic Society and played a great part in the development of this organization, which is one of the best in existence. For many years he was active in the Kansas City Society of Otolaryngology. He was one of the original organizers of the American Society of Ophthalmologic and Otolaryngologic Allergy and the Hansel Foundation, of which he was president at the time of his death.

The College, through the Board of Regents of which he was a member at the time of his death, extends to Mrs. Black and family its deepest sympathy in their bereavement. The death of Doctor Black is a great loss, not only to the College and to those who enjoyed his friendship, but also to the entire medical world, many of whom derived so much benefit through their contacts with him. Doctor Black was a true friend, a grand fellow, well-met and admired. His friends will miss him. His memory lives on.

His survivors are: his widow, Mrs. Helen T. Black of Kansas City, Missouri; and two sons, Durrill M. Black of Johnstown, Colorado, and William Byron Black, Jr., of Houston, Texas.

IN MEMORIAM

ARTHUR C. KALISCH

Arthur C. Kalisch, M. D., charter member of the Pennsylvania Allergy Association and member of the American College of Allergists died suddenly Wednesday, October 5, 1949, at his home in York, Pennsylvania, as a result of a cerebral hemorrhage.

Dr. Kalisch was born in York, Pennsylvania, on July 22, 1906, and attended the York High School where he was the salutatorian. His collegiate and medical training was at the Johns Hopkins University and medical school, graduating in 1928 and 1932, respectively. He interned at the Jewish Hospital in Brooklyn, New York and had a residency in pediatrics there in 1933. He completed a residency in medicine at the Mt. Sinai Hospital in Baltimore, Maryland, in 1934 and a residency in pathology at the Montefiore Hospital in Bronx, New York, in 1935. He opened offices for practice in York in 1937.

Dr. Kalisch was an assistant in medicine and worked in the allergy clinic at Mt. Sinai Hospital in Baltimore. He attended instructional courses of the American College of Allergists, New York Postgraduate School and American College of Physicians. He was Chief of the Allergy Clinic at the York Hospital and instructor in Allergy in the school of nursing.

He was a fellow of the American Medical Association, member of York County and Pennsylvania Medical Societies. He was a member of both the American Academy of Allergy and The American College of Allergists. He belonged to the University Club of York. Stamp collecting was a hobby.

While in the armed service in World War II, he published a survey of allergy in the Mediterranean theatre of Operations.

Dr. Kalisch is survived by his wife, Harriet, and a son, Arthur C. Kalisch, Jr., aged eight. His death was a shock to all members of the Pennsylvania Allergy Association and other organizations. The College has lost a very active and valuable member, and the officers extend their deepest sympathy to the family.

Mrs. Kalisch, in reply to a letter of condolence wrote: "I hope the College will continue to maintain its high standards in Allergy—to which my husband dedicated his life."

THE PARENTERAL USE OF NEO-ANTERGAN

(Continued from Page 71)

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322 South 16th Street

News Items

CLEVELAND ALLERGY SOCIETY

At a recent meeting of the Cleveland Allergy Society, the following officers were elected for the coming year: President, Dr. Joseph L. Vinocur; Vice President, Dr. Lewis E. Abram; Secretary-Treasurer, Dr. Benjamin Nozik.

SOUTHWEST ALLERGY FORUM

The annual meeting of the Southwest Allergy Forum will be held at the Hotel Peabody, in Memphis, on April 2, 3, and 4, 1950. The local allergy society, the Midsouth Allergy Forum, will act as host for the Southwest meeting.

LOS ANGELES SOCIETY OF ALLERGY

At the meeting of the Los Angeles Society of Allergy held November 25, 1949, the following officers were elected: President, Frank G. Crandall, Jr., M.D.; Vice-President, M. Coleman Harris, M.D.; and Secretary-Treasurer, Norman M. Shure, M.D.

MEXICAN SOCIETY OF ALLERGISTS INSTRUCTIONAL COURSE IN ALLERGY

The Mexican Society of Allergists conducted an Instructional Course in Allergy from January 30 to February 18, 1950. This course was sponsored by the Graduate School of Medicine of the National University of Mexico.

The Mexican Society of Allergists held its Fourth National Congress on Allergy from February 6 to 11.

AMERICAN COLLEGE OF CHEST PHYSICIANS

The First International Congress on Diseases of the Chest will be held at the Carlo Forlanini Institute, Rome, Italy, September 17-20, 1950, under the auspices of the Council on International Affairs of the American College of Chest Physicians and the Carlo Forlanini Institute, with the patronage of the High Commissioner of Hygiene and Health, Italy, in collaboration with the National Institute of Health and the Italian Federation Against Tuberculosis.

Physicians who are interested in attending the Congress should communicate at once with Dr. Chevalier L. Jackson, Chairman of the Council on International Affairs, American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Illinois, U.S.A., or with Professor A. Omodei Zorini, Carlo Forlanini Institute, Rome, Italy.

STERILITY AWARD

The American Society for the Study of Sterility is offering an annual award of $1,000, known as the Ortho Award, for an essay on the result of some clinical or laboratory research pertinent to the field of sterility. Competition is open to those who are in clinical practice as well as to individuals whose work is restricted to research in basic fields or full-time teaching positions. The prize essay will appear on the program of the forthcoming meeting of the American Society for the Study of Sterility, which is to be held at the Sir Francis Drake Hotel in San Francisco on June 24 and 25, 1950.

Full particulars may be obtained from the Secretary, Dr. Walter W. Williams, 20 Magnolia Terrace, Springfield, Massachusetts. Essays must be in his hands by April 1, 1950.

NEWS ITEMS

PSYCHOTHERAPY COURSE FOR ALLERGISTS

Dr. Sandor Rado, Clinical Professor of Psychiatry, and Director of the Psychoanalytic Clinic for Training and Research, Columbia University, will give a course for qualified physicians, entitled, "Psychotherapy for Allergists," beginning Monday, November 6, to Friday, November 10, 1950. This course is being given with the co-operation of The American College of Allergists. Other members of the staff of the Psychoanalytic Clinic will also participate in the program of the course. Lectures and clinics will be held from 9:00 a.m. to 12:30 p.m. and from 2:00 p.m. to 5:00 p.m. daily. It is possible that evening round-table discussions may be arranged.

The purpose of this course is to increase the physician's understanding of the human organism by blending the elements of psychodynamics with the basic medical sciences upon which this understanding rests. An attempt will be made to discuss emotional maladjustment as a factor in the comprehensive pathology of the allergic patient; to familiarize the physician with the psychological aspects of the patient-physician relationship and with the techniques of the minor psychotherapy of the allergic patient.

Physicians practicing in the field of allergy will be given preference in the order of application. Registration will be limited to fifty students. The registration fee is $100.00. Details may be obtained from Dr. Harold A. Abramson, 133 East 58th Street, New York, New York.

PITTSBURGH ALLERGY SOCIETY

At the regular meeting of the Pittsburgh Allergy Society, held November 21, 1949, the following officers were elected for 1950-1951: President, Dr. Mayer A. Green; Secretary-Treasurer, Dr. Sylvia M. Wechsler. The following committee members were appointed: Executive Committee—Dr. L. H. Criep, Dr. J. A. Mansmann, Dr. L. L. Bartlett, and Dr. M. A. Green; Membership Committee—Dr. Florence Kline, Chairman; Dr. Philip Blank, and Dr. R. G. Hamilton; Program Committee—Dr. A. R. McCormick, Chairman; Dr. J. W. Hampsey, Dr. L. J. King, and Dr. J. W. Schoolnic; Pollen Committee—Dr. E. P. Claus, Chairman; Dr. J. A. Mansmann, Dr. R. W. Wilson, and Dr. A. H. Neidorff.

* * *

The Allergists Supply Company, 458 Broadway, New York City, announces the development of a new process for graduating their Allergy Barrels and all glass Tuberculin Syringes, which will help reduce breakage.

* * *

I. Wiener, M.D., F.A.C.A., announces the opening of offices at 13011 West McNichols Road, Detroit, Michigan, for the practice of Allergy and Internal Medicine.

EMOTIONAL TRAUMATA

(Continued from Page 107)

5. Miller, Hyman, and Baruch, Dorothy W.: Psychosomatic studies of children with allergic manifestations. I. Maternal rejection: a study of sixty-three cases. Psychosom. Med., 10:275-278, (Sept.-Oct.) 1948.
6. Miller, Hyman, and Baruch, Dorothy W.: A study of hostility in allergic children. Presented at the annual meeting, American Orthopsychiatric Association, Chicago, April, 1949.
7. Miller, Hyman, and Baruch, Dorothy W.: Maternal rejection in allergic children. Presented in the Round Table on Pediatric Allergy at the annual meeting, American College of Allergists, Chicago, April, 1949.
8. Mitchell, J. H., and Curran, C. A.: A method of approach to psychosomatic problems in allergy. West Virginia M. J., 42:1, 1946.

201 S. Lasky Drive